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

PMTA Scientific Review: Technical Project Lead (TPL)

SUBMISSION INFORMATION			
Applicant	22nd Century Group, Inc.		
Product Manufacturer	NASCO Products, LLC		
Submission Date	December 4, 2018	**FDA Receipt Date**	December 4, 2018
Cross-referenced Submission[1]	**Cross-referenced STN**	**Primary STN(s)**	
	(b)(4)	Applies to all STNs	

NEW TOBACCO PRODUCTS	
PM0000491: Moonlight ®[2]	
Product Category	Cigarettes
Product Sub-Category	Combusted, Filtered
Package Type	Hard pack
Package Quantity	20 per pack
Characterizing Flavor	None
Length	83 mm
Diameter	7.9 mm
Ventilation	13%
PM0000492: Moonlight ® Menthol[2]	
Product Category	Cigarettes
Product Sub-Category	Combusted, Filtered
Package Type	Hard pack
Package Quantity	20 per pack
Characterizing Flavor	Menthol
Length	83 mm
Diameter	7.9 mm
Ventilation	13%

[1] The application contains a valid and active cross-reference, which contains appropriate authorization for the applicant to reference the entire file or certain sections thereof.

[2] On December 4, 2018, FDA received original PMTAs for VLN™ King and VLN™ Menthol. On October 2, 2019, the applicant submitted a proposed name change for the products to Moonlight and Moonlight Menthol, respectively. The scientific reviews reflect the proposed names (VLN™ and VLN™ Menthol) in the original PMTA submissions.

DISCIPLINES REVIEWED	Primary Reviewer(s)	DATE OF REVIEW
Behavioral and Clinical Pharmacology	**Kia Jackson**	**October 29, 2019**
Chemistry	**An Vu**	**October 29, 2019**
Environmental Science	**Rudaina Alrefai-Kirkpatrick**	**October 29, 2019**
Engineering	**Robert Meyer**	**October 30, 2019**
Epidemiology	**Joanne Chang**	**October 29, 2019**
Medical	**Anna-Sophie Weidner**	**October 30, 2019**
Microbiology	**Prashanthi Mulinti**	**October 30, 2019**
OCE – BIMO	**Tara Singh**	**October 30, 2019**
OCE – Manufacturing/Lab	**Eugene Chang**	**October 30, 2019**
OCE – DPAL	**Matthew Rohit**	**October 30, 2019**
Social Science	**Katherine Margolis**	**October 29, 2019**
Statistics	**Chunfeng Ren**	**October 30, 2019**
Toxicology	**Jonathan Fallica**	**October 31, 2019**

Recommendation
☒ Issue marketing order letters
☐ Issue denial letters

Technical Project Lead (TPL):

Iilun C. Murphy -S
2019.11.20 15:52:43 -05'00'

Iilun Murphy, M.D.
Director
Division of Individual Health Science, Office of 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)

Digitally signed by Matthew R. Holman -S
Date: 2019.11.22 16:13:51 -05'00'

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

TABLE OF CONTENTS

Table of Tables

1. EXECUTIVE SUMMARY

On December 4, 2018, FDA received PMTAs (PM0000491-PM0000492) from 22nd Century Group Inc. (also referred to as: applicant/22nd Century) for two products -- VLN™ King and VLN™ Menthol King cigarettes -- to be marketed in the U.S. upon receipt of a marketing authorization. Of note, on October 2, 2019, FDA received an amendment (PM0000594) requesting a name change for their proposed products from VLN™ King and VLN™ Menthol King cigarettes to Moonlight® and Moonlight® Menthol cigarettes, respectively. As this name change request was received after the scientific review had been completed, the related documents refer to the proposed products by the original proposed name VLN™ King and VLN™ Menthol King.

The VLN™ King and VLN™ Menthol King cigarettes (together referred to as VLN™ cigarettes) are conventional cigarettes developed with the purpose of reducing cigarette smokers' exposure to nicotine. The VLN™ King and VLN™ Menthol King cigarettes have similar adverse health risks as NNC cigarettes if used in a similar manner given that the proposed new products differ from NNC cigarettes only in nicotine content. Any potential reduction in risk in the proposed new tobacco product comes from reducing nicotine exposure and cigarette consumption. The applicant states that these cigarettes contain at least 95% less nicotine in the tobacco than typical commercial cigarettes.

A new tobacco product, including a tobacco product modified in any way ("including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient") after February 15, 2007, generally requires premarket authorization from FDA (sections 910(a)(1)(B) and 910(a)(2)(A)).

A PMTA must be submitted to FDA under section 910(b) of the FD&C Act and a marketing authorization order must be received from FDA under section 910(c)(1)(A)(i) prior to marketing any new tobacco product, unless FDA has found that the new tobacco product is substantially equivalent to a tobacco product commercially marketed in the U.S. as of February 15, 2007 (see section 910(a)(2)(A)(i)) or is exempt from a substantial equivalence determination pursuant to regulation (see section 910(a)(2)(A)(ii)).

FDA will deny a PMTA and issue a no marketing authorization order stating that the product may not be introduced or delivered for introduction into interstate commerce under section 910(c)(1)(A)(ii) where FDA finds that:

- there is a lack of a showing that permitting the product to be marketed would be appropriate for the protection of the public health;
- the methods, facilities, or controls used in manufacturing, processing, or packing do not conform to manufacturing regulations issued under section 906(e) (21 U.S.C. 387f(e));
- based on a fair evaluation of all material facts, the proposed labeling is false or misleading; or

- it is not shown that the product complies with any tobacco product standard in effect under section 907 (21 U.S.C. 387g), and there is not adequate information to justify deviation from the standard.

The statute provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Scientific review of these applications has demonstrated the following:

- There is sufficient information to characterize the product composition and design.
- There are adequate process controls and quality assurance procedures to help ensure VLN™ cigarettes are manufactured consistently to meet the applicant's specifications.
- The toxicological profiles of VLN™ King and VLN™ King Menthol are essentially identical except for the quantity of menthol. Overall toxicant-associated noncancer hazards and cancer risks due to use of VLN™ cigarettes are likely similar to the application's six comparator NNC cigarettes that represent approximately 25% of the cigarette market, assuming that the VLN™ cigarettes will be used in the same way as the comparators. Evidence from clinical studies may indicate that the associated noncancer hazards and cancer risks could be lower compared to marketed cigarettes, as users of products very similar (SPECTRUM very low nicotine content [VLNC] cigarettes) to the VLN™ cigarettes tend to decrease their cigarettes per day (CPD) and puffing volumes if they switch from NNC cigarettes to VLNC cigarettes. This suggests that toxicological impacts may be proportionately decreased if users were to switch, due to a reduction in CPD. Clinical biomarkers of exposure (e.g., NNAL, CO, PheT, 3-HMPA) tend to support that acute and complete switching is associated with harmful and potentially harmful constituents (HPHC) and CPD reductions, whereas gradual switching is not, suggesting that reduction in HPHCs, and therefore associated hazards or risks, are likely via reduction in CPD.
- Noncancer hazards and cancer risks to dual users of tobacco products, where at least one product is VLN™ King or VLN™ Menthol King cigarettes, are also likely to be similar or lower than smoking the six commercially marketed cigarette comparators, to the extent that the use of the other products, including nicotine replacement therapy (NRT) that are used with VLN™ King or VLN™ Menthol King cigarettes, is less harmful than the six commercially marketed cigarette comparators. However, using VLN™ cigarettes compared to quitting tobacco use or completely switching to NRT would increase harm, as toxicant exposures would be similar to exposure resulting from the use of NNC cigarettes.
- The pharmacokinetic (PK) profile of VLN™ cigarettes indicates a lower abuse liability than the applicant's usual brand-normal nicotine content (UB-NNC) cigarette comparator.

- VLN™ cigarettes are associated with lower positive subjective effects ratings (e.g., liking, pleasant, satisfaction) compared to UB-NNC cigarettes, reducing their abuse liability for youth and non-smokers. As menthol in NNC cigarettes facilitates experimentation and progression to regular smoking, it is unknown to what degree smoking VLN™ Menthol King cigarettes may influence progression to regular smoking compared to NNC menthol cigarettes in new and inexperienced users, particularly youth and young adults. Menthol and non-menthol NNC smokers who choose to switch to VLNC cigarettes would experience the benefit of significantly reducing their overall exposure to nicotine, potentially reducing their overall smoking, and subsequently, their exposure to non-nicotine HPHCs. Given that current adult smokers are the intended population for VLN™ cigarettes, reduced likelihood of use among adult smokers is likely to reduce youth access to these products and their availability for youth experimentation.
- Youth may believe that VLNC cigarettes might be "safer" than NNC cigarettes, and youth who experimented with VLN™ cigarettes could transition to NNC cigarette smoking, although likelihood of uptake of VLN™ cigarettes by youth is anticipated to be low due to low appeal and abuse liability. The applicant did not provide information on how menthol VLN™ smoking could impact the likelihood of VLN™ use by youth, however, in the adult study of VLN™ Menthol King data showed these cigarettes have lower positive subjective effects than UB-NNC cigarettes although the reduction is less than compared to VLN™ King cigarettes. 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. 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.
- Findings from the literature indicate that individuals who smoke VLNC cigarettes demonstrate either no significant differences in smoking topography relative to those who smoke UB-NNC or NNC cigarettes or reductions in tobacco smoke exposure (e.g., lower total puff volume); smoking VLNC cigarettes may lead to an overall reduction in CPD compared to smoking UB-NNC cigarettes.
- Low subjective appeal, along with increased craving and withdrawal, may prevent current smokers from fully transitioning to VLN™ cigarettes. Data from the literature suggest that those who do switch to VLNC cigarettes reduce their exposure to nicotine and a range of non-nicotine HPHCs, may smoke fewer CPD, may reduce their nicotine dependence levels, and increase their quit attempts compared to those who continue to smoke UB-NNC cigarettes. It is anticipated that smokers who switch to VLN™ cigarettes and reduce their overall CPD would experience the greatest benefit of reducing their exposure to nicotine and non-nicotine HPHCs, though VLN™ smokers who do not reduce their CPD still reduce exposure to nicotine.
- Switching to VLNC cigarettes may facilitate abstinence in smokers by increasing motivation to quit and quit attempts. Concurrent use of NRT and behavioral intervention may improve

these outcomes. However, among menthol smokers who switch to VLNC cigarettes, the potential effect on cessation may be less likely than with non-menthol VLNC cigarette smokers. Based on literature extrapolated from NNC menthol cigarettes, the reduced likelihood of cessation may occur even in smokers motivated to quit and who concurrently use pharmacotherapy for cessation. Nonetheless, both menthol and non-menthol NNC smokers who switch to VLNC cigarettes could experience the benefits of reduced exposure to nicotine, potential reductions in dependence therefore leading to reductions in CPD, increased quit attempts, and potential quitting in some smokers compared to smoking their UB-NNC cigarettes.

- Literature indicates that dual use and noncompliance with smoking VLNC cigarettes in clinical studies is high; however, nicotine exposure remains significantly reduced in participants who smoke VLNC cigarettes compared to NNC cigarettes. Despite high levels of dual use/noncompliance, data suggest that smoking VLNC cigarettes can lead to an overall reduction in CPD compared to smoking UB-NNC cigarettes.
- 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 the UB-NNC cigarettes, would likely reduce their overall CPD, and would experience the effects of reduced dependence on nicotine. Some consumers, in particular those who dual use VLNC and UB-NNC cigarettes, may not decrease their overall cigarette consumption; however, dual use of other nicotine-containing products, such as NRT or electronic nicotine delivery systems (ENDS), may aid in reducing CPD.
- There have been no specific, short-term health-related or product quality issues unique to VLN™ cigarettes in the clinical studies or the published literature. 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 to those associated with NNC cigarettes, given that the proposed products differ from NNC cigarettes only in the nicotine content. As such, it is likely that the health risks of polytobacco use will not be any different for VLN™ cigarettes compared to NNC cigarettes.
- If smokers who switch to VLN™ cigarettes decrease their use and/or ultimately quit, there would likely be improved health benefits. If, on the other hand, cigarette smokers who completely switch to VLN™ cigarettes use them in the same way as NNC cigarettes, it is possible that they may have weight gain, but with the added adverse health consequences of continued smoking. Based on existing clinical studies, the likelihood of this latter scenario is likely low.
- Smoking increases the risk of cardiovascular disease and thrombosis. While in vivo and in vitro studies have indicated that VLN™ cigarettes may cause greater platelet activation compared to cigarettes with a higher nicotine content, which may contribute to potential increased risk of thrombosis compared to other cigarettes, adverse event data are insufficient to draw meaningful clinical conclusions regarding whether there is increased risk of thrombosis. At this time we do not have clinical information raising concern that there is substantive increased risk of thrombosis from use of VLNC cigarettes. If additional data becomes available elucidating this relationship, further consideration of risk and benefit to the population as a whole is warranted. Post market reporting requirements should include submitting any serious or unexpected adverse experiences reported to 22nd

Century as well as summarizing any new significant findings on publications not previously reported relevant to VLN™ cigarettes.

- While smokers who completely switch to VLN™ cigarettes may experience nicotine withdrawal, in brief exposure VLNC cigarette studies craving and withdrawal were suppressed relative to baseline following overnight abstinence, indicating that withdrawal will likely be less in people switching to VLN™ cigarettes than in those who quit smoking cold turkey (e.g., Barrett, 2010; Rose, Salley, Behm, Bates, & Westman, 2010; Tidey, Rohsenow, Kaplan, Swift, & Ahnallen, 2013). Adverse event data from company-sponsored studies and from the published literature are limited but suggest that some adverse events may relate to nicotine withdrawal. There is little experience with VLN™ cigarettes to determine whether they may have adverse public health consequences beyond relapse to NNC cigarettes or other nicotine sources, such as ENDS, or the use of other substances to mitigate withdrawal symptoms.
- Non-users who are involuntarily exposed will likely experience similar adverse health effects as exposure to tobacco smoke from NNC cigarettes.
- Although the data for VLN™ cigarette uptake by never smokers, former smokers, and youth is limited, similar products have been available on the U.S. market previously and uptake by youth and current nonsmokers was not evident and therefore does not likely appear to be of significant concern. Postmarket reporting may help to ensure this does not become problematic after the proposed products are marketed in the U.S. The population most likely to use VLN™ cigarettes is current NNC cigarette smokers, especially those motivated to quit. Additionally, the applicant will be required to monitor consumer use patterns and demographic information and provide FDA with regular reports.

Overall the VLN™ King and VLN™ King Menthol cigarettes meet the following criteria specified in section 910(c)(2) of the FD&C Act:

1. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in section 906(e)[3] of the FD&C Act.
2. Based on a fair evaluation of all material facts, the labeling is not false or misleading in any particular.
3. The products do not fail to conform to a tobacco product standard in effect under section 907 of the FD&C Act.
4. Permitting the marketing of the products is at this time appropriate for the protection of the public health, as described in section 910(c)(4) of the FD&C Act.

I recommend that FDA grant marketing authorization for the proposed products that are the subject of PM0000491 and PM0000492 for the reasons described above.

[3] FDA has not yet promulgated any regulations under Section 906(e) of the FD&C Act.

2. REVIEW OF PMTAs

2.1. Regulatory History

On December 4, 2018, FDA received two PMTAs (PM0000491-PM0000492) from 22nd Century for VLN™ King and VLN™ Menthol King cigarettes (together referred to as VLN™ cigarettes). On December 11, 2018, FDA received an unsolicited amendment (PM0000493) containing all content from the original PMTAs, including missing appendices from the original submissions. On December 19, 2018, FDA issued an Acknowledgement letter and conducted a teleconference with the applicant to convey technical issues with the submission files and options to rectify the issues needed to proceed with review. In response, FDA received an amendment (PM0000497) on January 10, 2019, requesting the withdrawal of amendment PM0000493 and resubmitting the original PMTAs in an FDA-accessible format. On January 24, 2019, FDA issued a Filing letter. On February 11, 2019, FDA received an amendment (PM0000499) providing new analytical test data. On February 19, 2019, FDA conducted a teleconference requesting information to clarify product design, manufacturing acceptance criteria, HPHC testing regimens, and contact information. In response, FDA received an amendment (PM0000603) on February 25, 2019.

On March 14, 2019, FDA received an amendment (PM0000506) containing a revised report related to the Consumer Perception and Intention Study, and data pertaining to a 9-month stability study. On March 15, 2019, FDA received two amendments (PM0000507, PM0000508) correcting previously submitted HPHC data, updating the quantitative risk assessment (QRA), and providing results from the Menthol Abuse Liability Study Report. On March 20, 2019, FDA received an amendment (PM0000509) clarifying information in the tobacco-specific nitrosamines (TSNAs) stability study report. On April 3, 2019, FDA received an amendment (PM0000511) providing raw data for the Consumer Perception Study. On April 4, 2019, FDA issued a Major Amendment letter notifying the applicant that the March 14, 2019, and March 15, 2019, amendments received contain a substantial amount of new data that has not been previously submitted to or reviewed by FDA, such as new data from a previously unreported study or detailed new analyses of previously submitted data. This major amendment was reviewed by the review team and TPL.

On June 27, 2019, FDA received an amendment (PM000514) that contained: 1. 12-month storage stability and water activity study results, 2. Summary reviews of four recently published studies available in the public literature involving VLNC cigarettes. As this amendment was received late in the scientific review cycle, this minor amendment was processed as a TPL-only review as the information submitted does not impact the scientific conclusions previously made by the review team. On July 18, 2019, FDA received an amendment (PM0000519) that contained a new clinical study report: A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes. As the amendment contained significant amount of new data that required substantial additional FDA review team and TPL time, the amendment was determined to be a major amendment. A teleconference (t-con) was held with the applicant on August 2, 2019 to convey this information and a request was made to 22nd Century for

additional clarifying information to be submitted related to the serious adverse experience that was reported associated with the new clinical study. On August 7, 2019, FDA received an amendment (PM0000524) that contained additional narrative related to the serious adverse experience reported in PM0000519. A t-con was held on September 9, 2019, with 22nd Century requesting clarification on the quantitative consumer perception study. An amendment (PM0000544) was submitted on September 13, 2019, explaining discrepancies observed between the study protocol and data submitted.

A t-con was held with 22nd Century on September 23, 2019, with the applicant to discuss the potential for the name VLN™ to render the product a modified risk tobacco product given public communication available on applicant websites associating the product VLN™ and the words "very low nicotine". A press release dated December 5, 2018 announcing the filing of the PMTA is titled "22nd Century Files Premarket Tobacco Application (PMTA) with the FDA." The press release explains that the application is for cigarettes to be marketed "under the proposed brand name VLN™ (the product name is subject to FDA approval). 22nd Century's proposed VLN™ cigarettes – the subject of the PMTA – are made with 22nd Century's proprietary VLN™ tobacco and, as a result, contain very low levels of nicotine" (https://ir.xxiicentury.com/press-releases/detail/356/22nd-century-files-premarket-tobacco-application-pmta). The December 5, 2018 press release announcing the filing of an PMTA for "Very Low Nicotine Content Cigarettes" can also be found on the firm's website (https://ir.xxiicentury.com/press-releases/detail/356/22nd-century-files-premarket-tobacco-application-pmta). At this time, there are no modified risk orders in effect for these products. Additionally, a change in name does not create a new tobacco product. Therefore, an applicant may change their product name for many reasons, including if they are pending a decision on an MRTP application but seek to market a new product authorized under a PMTA. On October 2, 2019, 22nd Century submitted an amendment (PM0000549) proposing a name change from VLN™ King and VLN™ Menthol King cigarettes to Moonlight® and Moonlight® Menthol cigarettes respectively.

Table 1: Amendments Submitted by Applicant

STN	Date Received	Amendment Type	Content
PM0000493	12-11-2018	Major	N/A – Amendment withdrawn
PM0000497	01-10-2019	Major	Majority of the PMTA submission including large number of files related to study documents, literature search/references, responsive electronic documents
PM0000499	02-11-2019	Minor	Analytical test data
PM0000502	02-25-2019	Minor	Analytical information, study contact information
PM0000506	03-14-2019	Major	Revised report and data pertaining to the Consumer Perception and Intention

			Study; 9-month storage and stability study results
PM0000507	03-15-2019	Minor	HPHC correction data, updated QRA
PM0000508	03-15-2019	Major	A new clinical study report: Evaluation of the Abuse Liability of Very Low Nicotine Mentholated Cigarettes
PM0000509	03-20-2019	Minor	TSNA in stability study report
PM0000511	04-03-2019	Minor	Raw data for Consumer Perception Study
PM0000514	06-27-3019	Minor	12-month storage stability and water activity study results; Reviews of four recently published VLNC cigarettes studies
PM0000519	07-18-2019	Major	New six-week clinical study report: A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes
PM0000524	08-07-2019	Minor	Additional narrative related to the serious adverse experience reported in PM0000519
PM0000544	09-13-2019	Minor	Supporting documentation for the quantitative consumer perception study
PM0000549	10-02-2019	Minor	Proposed name change and revised labeling

2.2. Product Composition, Design, and Manufacturing

22nd Century references products it previously manufactured that are similar to the proposed products in PM0000491-PM0000492 to support the requested authorization; the previously manufactured products were labeled as SPECTRUM and PARE cigarettes. The applicant's very low nicotine content (VLNC) tobacco was developed in 1998 and has been used for producing cigarettes under different names, including SPECTRUM and PARE. In 2011, the applicant developed the SPECTRUM line of research cigarettes in collaboration with the National Institute on Drug Abuse (NIDA), FDA, the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC).

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 contents. 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."

2.2.1. Tobacco Ingredients

The two VLN™ cigarette tobacco products contain an (b)(4) tobacco blend that consists of approximately (b)(4) and (b)(4). The blend also contains (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. (b)(4)

Unlike typical American blended cigarette tobacco, which contains a mixture of Bright, Burley, Oriental, and reconstituted tobaccos, (b)(4) tobacco blend consists of all (b)(4) tobacco. (b)(4) To address this concern, the applicant provided HPHC data for the VLN™ cigarette tobacco products including all abbreviated HPHCs recommended for cigarette mainstream smoke.[4] See Section 2.3.1. of this review for evaluation of HPHC data.

The Vector 21-41 strain of (b)(4) tobacco is produced through genetic engineering of quinolinic acid phosphoribosyltransferase (QPTase), a key enzyme in the biosynthetic pathway of nicotine production and related alkaloids. Based on the toxicology review, no chronic or sub-chronic toxicological assessments in any nonclinical species are currently available for the transgenic tobacco contained in VLN™ cigarettes; therefore, the consequences of inhaling transgenic tobacco from the transgenic plants are unknown. However, SPECTRUM Nicotine Research Cigarettes (NRCs), which are similar to VLN™ cigarettes, have been used in short-term clinical studies without any apparent alterations in smokers' health in comparison to their UB-NNC cigarette to date. In addition, as noted by the applicant, the only new protein that is expected to be produced is neomycin phosphotransferase encoded by *nptII*; according to the applicant, neomycin phosphotransferase has no significant homology with proteins listed as food allergens or toxins (PMTA Section IV. Descriptive Information). From a toxicology perspective,

[4] FDA Draft Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act, 2012.

the breakdown of neomycin phosphotransferase during tobacco processing and burning is a reasonable expectation and therefore unlikely to raise concerns.

Nonetheless, tobacco blend combustion is associated with HPHC production, impacting HPHC yields. In this case, the only tobacco variety in VLN™ King and VLN™ Menthol King cigarettes appears to be low alkaloid (b)(4) tobacco. (b)(4) tobacco is typically associated with elevated nitrogen, ammonia, and nitrogen oxides, which can serve as precursors in the formation of TSNAs such as NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and NNN (n-nitrosonornicotine) (Ding et al., 2006; Ding et al., 2008; D. Hoffmann, Djordjevic, & Hoffmann, 1997; D. H. Hoffmann & Hoffmann, 2001). However, given the disruption in nicotine biosynthesis in Vector 21-41 (b)(4) tobacco, it appears that nornicotine, total alkaloids, and TSNAs are partially reduced compared to wild-type tobacco plants. The toxicology review states that while inferences based on the tobacco blend in VLN™ cigarettes could be further discussed regarding specific HPHCs, such as TSNAs, the blend information alone is insufficient to make toxicological conclusions. As such, the applicant provided HPHC data for VLN™ King and VLN™ Menthol King cigarettes, which are further discussed below. In brief, the HPHC data for both VLN™ cigarettes indicates that noncancer hazards and cancer risks are likely similar to or slightly lower than NNC cigarettes, based on HPHC comparisons to top market-share cigarettes.

For both VLN™ King and VLN™ Menthol King cigarettes, there are tobacco filler ingredients in the burned portion that may be associated with adverse health outcomes independent of the combustion process. Put differently, during cigarette combustion, ingredients may enter directly into the mainstream smoke (MSS), which can impact associated hazards and risks. Single ingredient additions and associated direct toxicities of concern are discussed in general below. Importantly, of the (b)(4) [redacted] This is noteworthy, as these ingredients, such are (b)(4) (b)(4), likely decompose into other byproducts, including HPHCs such as aldehydes during combustion, emphasizing the utility of the HPHC comparisons to inform ingredient toxicity evaluation. However, depending on the volatility of ingredients and temperature gradient moving away from the cigarette coal, it is possible for certain amounts of ingredients to enter the MSS unchanged by combustion (U.S. Department of Health and Human Services, 2014). In addition, an evaluation of tobacco filler ingredient quantities is not on its own sufficient to resolve any potential toxicity concerns, as the potency of some ingredients may be much greater or the effect level much smaller, relatively speaking. In other words, small quantities of ingredients may still contribute to toxicity concerns.

Available information on ingredients with known toxicities, such as (b)(4) (b)(4), indicate that they may be associated with adverse respiratory effects and may not undergo full transformation during combustion, thus posing potential added risk based on their inherent respiratory toxicities. Tobacco filler ingredients such as these, therefore, may be of toxicological concern, but are not addressed by the applicant regarding their potential adverse health effects or their contribution to the relative risk profiles in their comparative assessment. The toxicology review includes the available toxicity information for these ingredients. Other examples of ingredients that may be of concern include (b)(4)

(b)(4) which are associated with respiratory irritation; they are added to the filler in relatively larger quantities, but available data indicate that these ingredients may transform during combustion, thus contributing, in part, to HPHCs. In acknowledgement of the fact that ingredients could impact product hazards and risks, FDA notes that the applicant does not have access to the ingredient information for the commercially marketed NNC cigarette comparators, which, in part, likely explains the absence of potential ingredients from the applicant's submitted risk assessment. Based on information to date, which includes several reductions in HPHCs associated with respiratory toxicity, the toxicology review states that the tobacco filler ingredients are unlikely to increase the hazards or risks due to use of the VLN™ King and VLN™ Menthol King cigarettes compared to the use of commercially marketed NNC cigarettes. Furthermore, this conclusion is based on the potential of HPHC decreases to offset the inherent toxicities of the tobacco filler ingredients, assuming from a conservative perspective that some tobacco filler ingredients enter the MSS unchanged by combustion, at least to some extent. This concern may be further reduced if CPD reductions suggested by clinical data occur in practice, which would likely lead to comparative reductions in overall exposure and risks.

2.2.2. Non-tobacco Ingredients

The chemistry review notes that the applicant provided ingredients and their quantities for all casings, flavorings, components, and materials of the VLN™ cigarettes (see Table 2). Ingredient supplier, CAS number, purity, and function were also provided where available. The applicant also listed individual ingredients contained in complex purchased ingredients such as side seam adhesive, tipping adhesive, (b)(4) adhesives and (b) (4) adhesives. The ingredient information indicates that VLN™ cigarettes are composed of identical materials and components except for menthol in the filter of VLN™ Menthol King. As shown, these ingredients are commonly used in NNC cigarettes. Pyrolysis of many of these ingredients is known to produce HPHCs. For example, pyrolysis of (b)(4) generates mainstream smoke carbonyls and hydrocarbons such as formaldehyde, acrolein, and benzene. Decrease in (b)(4) has been shown to increase NNN, NNK, and 4-aminobiphenyl (Ding et al., 2008). (b)(4) decomposes to acrolein, whereas (b)(4) thermally degrades to propylene oxide. In addition, combustion of (b)(4) and (b)(4) forms acetaldehyde, formaldehyde, and benzene.

The VLN™ cigarettes contain approximately (b)(4) mg/cig of (b)(4). (b)(4) is a (b)(4) containing (b)(4) % (w/w) (b)(4). The addition of (b)(4) to tobacco can increase the quantity of nicotine by less than 0.0024 mg/cig and is not expected to have a significant impact on the nicotine delivery of the VLN™ cigarettes.

Table 2: Ingredients Other than Tobacco

Ingredient	CAS #	Function	Purity	Quantity (mg/cig)	
				VLN™ King	VLN™ Menthol King
(b)(4)					
(b)(4)					
(b)(4)					
(b)(4)					
Top Flavor					
(b)(4)					
(b)(4)		Cigarette Paper			
(b)(4)					
Tipping Paper		(b)(4)			
(b)(4)					
Filter Tow					
(b)(4)					
Plug Wrap					
(b)(4)					
Inner Plug Wrap					
(b)(4)					
(b)(4)		Filter			
(b)(4)					

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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The reported menthol delivery of VLN™ Menthol King is comparable to those of the two market-leading king-sized mentholated cigarette brands.

The VLN™ cigarettes are packed in flip-top hard packs in the same manner as NNC tobacco products, with 20 cigarettes per pack and 10 packs per carton. The materials used for packaging VLN™ cigarettes are listed in Table 3 below. The same pack and carton materials are used for both VLN™ tobacco products, but with different inks to differentiate between the menthol and regular products. All packaging components are provided by suppliers of packaging components for NNC tobacco products.

Table 3: Packaging Materials Used in VLN™ Cigarettes

Part Name	Identifying Number	Supplier	Quantity (g/pack)	
			VLN™ King	VLN™ Menthol King
Foil (aluminized paper)	(b)(4)			
Inner frame (cardboard)				
Tear-Tape				
Cellophane				
Hinge-Lid Label (cardboard)				
Carton (cardboard)				
Packaging Glue				
Case (corrugated cardboard)				

2.2.3. Product Design

The chemistry and engineering relevant product features of the VLN™ cigarettes are shown in Table 4. These features include reported cigarette weight, tobacco filler mass, and filler nicotine content as well as their target values and upper and lower limits. Although both are king-sized, there is a small difference in target cigarette weight between the two VLN™ tobacco products. (b)(4) This results in the target cigarette weight of (b)(4) mg for VLN™ Menthol King and (b)(4) mg for VLN™ King. The applicant established a target tobacco filler nicotine level of (b)(4) mg/g on a dry weight basis, with lower and upper limits of (b)(4) and (b)(4) mg/g respectively. The average reported tobacco filler nicotine contents of the 100 top selling U.S. cigarette brands and the top six U.S. market leading king-sized cigarette brands were determined to be 19.4 mg/g and 18.8 mg/g on a dry weight basis, respectively. Thus, the applicant's statement that VLN™ cigarettes statement have 95% less nicotine when compared to the top 100 U.S. cigarette brands and top 6 U.S. market leading king-sized cigarette brands appear to be accurate.

As stated in the engineering review, adequate target specifications and upper and lower range limits are provided by the applicant for the parameters listed in Table 4. The specifications provided do not raise any concerns from an engineering perspective, as they are recognized as specifications that are normal in the combustible filtered cigarette industry. Several range limit cells for the cigarette paper and filter are blank. The missing range limits for the paper are acceptable, (b)(4) (b)(4) , (b)(4) . The purchased materials are accepted based off certificates of conformance provided by each vendor. The filter parameters with blank range limit cells are acceptable as (b)(4) (b)(4)

Table 4: Cigarette Design Parameters

	VLN™ King		VLN™ Menthol King	
Parameter	Target	Range Limits	Target	Range Limits
Package Quantity				
	20	N/A	20	N/A
Overall Cigarette				
Length (mm)	(b)(4)			
Diameter (mm)				
Puff Count				
Draw Resistance (mm H2O)				
Burn Rate (mm/min)				
Cigarette Mass (mg)				
Cut Size (mm)				
Tobacco				
Filler Mass (mg)	(b)(4)			
Rod Density (g/cm3)				
Moisture (%)				
Filler nicotine dry weight basis (mg/g)				
Cigarette Paper				
Base Paper Basis Weight (g/m2)	(b)(4)			
Base Paper Porosity (CU)				
Band Diffusion (cm/s)				
Band Width (mm)				
Band Space (mm)				
Filter				
Total Denier (g/9000m)	(b)(4)			
Denier Per Filament (DPF)				
Density (g/cm3)				
Draw Resistance (mm H2O)				
Length (mm)				
Ventilation (%)				
Filter Efficiency (%)				
Filter Weight (mg)				
Tipping Paper				
Length (mm)	(b)(4)			

N/A – not applicable; N/P – not provided

2.2.4. Manufacturing, Process, and Controls

VLN™ cigarettes are manufactured at NASCO Products, LLC located at 321 Farmington Road, Mocksville, North Carolina 27028. This facility is a wholly owned subsidiary of 22nd Century Group, Inc. The applicant provided flowcharts for every manufacturing step including (b)(4) (b)(4) (b)(4) .

According to the applicant's manufacturing information, (b)(4)

(b)(4) . This manufacturing issue was referred to OCE for further investigation during the manufacturing site inspection. During the April 2019 inspection of the applicant's NASCO manufacturing facility, NASCO's general manager stated that (b)(4) (b)(4) (b)(4)

2.2.5. FDA Sample Testing

The 22nd Century referenced Tobacco Product Master File (TPMF) (b)(4) (and amendments (b)(4)) for all analytical methods used to test VLN™ and comparator cigarettes described in PM0000491-PM0000492. The owner of (b)(4) , Enthalpy Analytical, provided a letter dated November 16, 2018 authorizing CTP to reference (b)(4) in support of all submissions by 22nd Century. The chemistry TPMF review evaluates applicable test methods described in (b)(4) and referenced in PM0000491-PM0000492. No substantive issues were identified.

Four batches of VLN™ King and four batches of VLN™ Menthol King were analyzed by Enthalpy Analytical via validated testing methods for tobacco filler nicotine content, physical parameters, and tar, nicotine, and carbon monoxide (TNCO) measured under the International Organization for Standardization (ISO) smoking regimen. The applicant analyzed an additional batch of the two VLN™ cigarettes for tobacco filler nicotine content and ISO TNCO. The tobacco nicotine content of all tested batches of the two VLN™ tobacco products met their nicotine specification of (b)(4) mg/g on a dry weight basis.

In accordance with section 910(b)(1)(E) of the FD&C Act, the applicant submitted 22 cartons of VLN™ King and 25 cartons of VLN™ Menthol King cigarettes to FDA's Southeast Tobacco Laboratory (STL) on December 4, 2018 in support of these PMTAs. Due to the reported nicotine levels of the two VLN™ cigarettes, CTP Office of Science (OS) requested that FDA's STL analyze each tobacco product to confirm the nicotine data submitted in the PMTAs. STL performed the requested analysis on February 26 and 27, 2019.

STL analyzed the VLN™ cigarettes to verify the nicotine data reported in the PMTAs. STL reported tobacco nicotine contents on an "as received" basis. Thus, "as received" tobacco nicotine contents of the two VLN™ cigarette products and the six market-leading king-sized comparator cigarette brands reported in the PMTAs are used for direct comparison. There are moderate differences between the STL and PMTA nicotine data for the VLN™ cigarettes. The STL data shows higher tobacco nicotine contents but lower nicotine deliveries than the PMTA data. However, the absolute nicotine quantity differences are minimal and are considered negligible relative to the broad market nicotine data. The STL data shows that the VLN™ cigarettes have 97-98% lower nicotine levels in tobacco and mainstream smoke than the top six comparator cigarette brands. Accordingly, the STL nicotine data also supports the applicant's statement that the proposed products contain 95% less nicotine.

Table 5: STL Nicotine Test Results of VLN™ Cigarettes

HPHC	STL Nicotine Data			PMTA Nicotine Data			% Change	
	Mean	SD	N	Mean	SD	N	STL Data vs. PMTA Data	STL Data vs. 6 Comparator Data
PM0000491 - VLN™ King								
Filler nicotine (mg/g)[a]	0.464	0.006	7	0.412	0.011	5	↑ 13	↓ 97
ISO nicotine (mg/cig)	0.01940[b]	0.00066	10	0.0246	0.0015	20	↓ 21	↓ 98
CI nicotine (mg/cig)	0.04447	0.00231	10	0.0566	0.0043	20	↓ 21	↓ 98
PM0000492 - VLN™ Menthol King								
Filler nicotine (mg/g)[a]	0.499	0.008	7	0.411	0.011	5	↑ 21	↓ 97
ISO nicotine (mg/cig)	0.02037	0.00116	10	0.0257	0.0012	20	↓ 21	↓ 98
CI nicotine (mg/cig)	0.04518	0.00213	10	0.0551	0.0047	20	↓ 18	↓ 98

CI – Canadian Intense machine smoking regimen
ISO - International Organization for Standardization machine smoking regimen

2.2.6. Product Stability

The applicant conducted stability studies. Samples were analyzed for tobacco filler nicotine and mainstream smoke TNCO and water under the ISO smoking regimen. The applicant provided the following information:

- Storage conditions prior to initiating testing: Stability studies were carried out under both standard (long-term) and accelerated conditions. These conditions follow the FDA Stability Testing Guidance and are appropriate.
    1. Standard evaluation: 25°C ± 2 °C, 60% relative humidity (RH) ± 5% RH for initially 9 months followed by 3 months for a total 12 months duration
    2. Accelerated evaluation: 40°C ± 2 °C, 75% RH ± 5% RH for 6 months

- Testing laboratory and their accreditation(s): Enthalpy Analytical laboratory with appropriate accreditation.
- Quantitative test protocols and methods used: Same as the HPHC test methods.
- Number of replicates: Twenty replicates were performed for each TNCO analysis, and seven replicates were performed for tobacco filler nicotine.
- Complete datasets: Complete stability datasets are provided in Appendix 11 of amendment PM0000497 and in amendments PM0000506, PM0000509, and PM0000514.
- Standard deviation(s): Standard deviations (SD) of the mean were also provided. Mean and SD values were verified to be correctly determined.
- Reference product datasets: 3R4F reference cigarette was tested alongside VLN™ cigarettes. 3R4F datasets are provided in Appendix 11 of amendment PM0000497. The applicant stated that all quality control samples were within limits. Moreover, the applicant's 3R4F results are comparable to those reported by the University of Kentucky and Roemer et al. (Roemer et al., 2012; University of Kentucky)

In the original application and amendments PM0000497 and PM0000506, the applicant stated that the stability studies for the two VLN™ cigarettes are on-going and submitted 9 months stability testing data measured under ambient (25°C ± 2 °C, 60% ± 5% RH) storage conditions and 6 months data measured under accelerated (40°C ± 2 °C, 75% RH ± 5% RH) storage conditions. The chemistry reviewer analyzed the data, including tobacco filler nicotine content and mainstream smoke TNCO and water content, and concluded that, except for water content in smoke, all stability yields relative standard deviation (RSD) values of the two VLN™ tobacco products under both ambient and accelerated storage conditions indicate acceptable variability after 9 and 6 months of product storage, respectively (see Section 3.9 of the chemistry review). However, the water reported in smoke varied moderately as shown by its RSD values (18-36%). Product storage conditions such as temperature, moisture (water content), and duration may affect the levels of TSNAs during storage. Based on the variability of water content in smoke of the two VLN™ cigarettes at various stability time points, FDA inquired during a teleconference on February 19, 2019 whether the applicant tested for TSNAs, over product storage time during stability studies. In response, the applicant submitted (PM0000509 and PM0000514) tobacco filler water activity (a_w) data measured under ambient, for 12 months, and accelerated storage conditions, for 6 months. a_w is a measure of the amount of water that is available for microbial growth in a product. Therefore, changes to a_w could potentially affect microbial growth. Microbial-mediated nitrite production is a key determinant of carcinogenic TSNA levels in the final tobacco product (Brunnemann, Prokopczyk, Djordjevic, & Hoffmann, 1996).

The applicant stated that as part of the storage stability study, retained samples were frozen for possible future analysis. The applicant indicated that the samples were defrosted and analyzed for a_w by Enthalpy Analytical to determine if there was sufficient water for microbial growth. Based on the data provided by the applicant, the a_w of all VLN™ cigarettes ranged from 0.465 – 0.589 under ambient conditions and 0.465 – 0.672 under accelerated product storage conditions. It is generally recognized that the a_w at which there is no microbial proliferation is <0.60 (Beuchat, 1983; Rockland et al., 1987). Additionally, as part of Amendment PM0000514,

the applicant provided adequate a_w data from a long-term stability study (twelve months under ambient conditions) measured over the proposed shelf life and recommended storage conditions of the two VLN™ products. Therefore, the a_w levels of the two VLN™ products under ambient and accelerated conditions, and the increases in a_w over the storage time of the products is not of concern from a microbiology perspective. Additionally, the chemistry review stated that the reported (single measurement) TSNA smoke yields of the two new VLN™ tobacco products are lower than the 6 comparator cigarettes, thus it is unlikely that TSNA deliveries of the two new VLN™ tobacco products would be higher than those of the market leading comparator cigarette brands during product storage. Therefore, the lack of TSNA data over complete storage time of the products does not raise any concerns from a chemistry perspective.

In summary, both chemistry and microbiology evaluation of the submitted stability data concluded that the applicant provided adequate information for all VLN™ cigarettes to demonstrate stability of the products over complete shelf life of the products.

2.2.7. Inspections of Manufacturing Facilities

FDA conducted an inspection of the applicant's manufacturing facility on April 23-26, 2019 to confirm the manufacturing information submitted in the PMTAs and determine whether the products can be consistently produced. No inspectional observations (Form FDA 483) were issued at the conclusion of the visit. The Establishment Inspection Report documents a "No Action Indicated" classification for this visit.

2.2.8. Summary of Composition, Design, and Manufacturing Findings

The engineering review concludes that the PMTAs contain adequate information with respect to the following:

- A complete characterization of the design parameters that are typical for NNC cigarettes other than nicotine content.
- An adequate description of manufacturing steps and quality control measures.
- Adequate process controls and quality assurance procedures to help ensure that the products meet manufacturing specifications for VLN™ cigarettes and that the products are manufactured in a consistent manner that minimizes the product quality variability.
- Performance testing to verify the product design.

As TPL, I agree with the engineering conclusions that these PMTAs contain sufficient information to characterize the product design and adequate processes and controls to help ensure that the products meet the manufacturer's specifications.

The chemistry review concludes these PMTAs contain adequate information with respect to the following:

- A complete list of uniquely identified components, ingredients, and additives by quantity in each new tobacco product as well as the applicable specifications and a description of the intended function for each.

- An adequate description of manufacturing/packaging steps and quality control measures in place.
- Sufficient information to assure FDA that the products meet manufacturing specifications for the tobacco products (specifically target nicotine levels) and that the products are manufactured in a consistent manner that minimizes product quality variability. The tobacco nicotine content of all 10 batches of VLN™ cigarettes met the nicotine specification of (b)(4) mg/g on a dry weight basis.
- Data on chemical endpoints establishing the stability of the product through the stated shelf life.
- Product analyses for verifying the product formulations.
- Testing data to demonstrate that the new products contain significantly lower levels of nicotine compared to major combusted cigarettes on the U.S. market.

As TPL, I agree with the chemistry conclusions that these PMTAs contain sufficient information to characterize the product composition and design and describe the manufacturing processes and controls that can affect the product composition, chemical stability, and HPHC levels to help ensure that the products meet the manufacturer's specifications.

The microbiology review concludes that the applicant provided adequate microbiology-related information to demonstrate product stability. As TPL, I agree with the microbiology conclusions.

The OCE manufacturing review identified no significant compliance issues during the manufacturing inspection conducted, and no observations were issued at the time of inspection.

2.3. Toxicological Risk Assessment

2.3.1. Harmful and Potentially Harmful Constituents (HPHCs)

2.3.1.1. General Overview

The applicant tested and reported HPHC data including all abbreviated HPHCs recommended for cigarette mainstream smoke under both ISO and Canadian Intense (CI) machine smoking regimens.[3] 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 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 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 carbon monoxide, 15% for nicotine and 20% for other HPHCs.[5]

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

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 smoke yields of acrylonitrile, 4-aminobiphenyl and ammonia are higher for both VLN™ cigarettes, whereas benzene yield is also higher for VLN™ Menthol King cigarettes. The applicant explained that the Vector 21-41 VLN™ tobacco technology that inhibits nicotine and TSNA production pathways may cause accumulation of ammonia and other nitrogen-containing constituents such as 4-aminobiphenyl in the plant. The change in the HPHC smoke yields is reviewed by toxicology and discussed below.

2.3.1.2. ISO Regimen HPHC Data

Per the applicant's submitted ISO regimen HPHC data and chemistry's TOST analysis, there are three analytically non-equivalent HPHC increases for VLN™ King cigarettes and four analytically non-equivalent HPHC increases for VLN™ Menthol King cigarettes in comparison to the average of the six commercially marketed NNC cigarette comparators. In both cases, acrylonitrile is increased (49% and 55% respectively), 4-aminobiphenyl is increased (21% and 19% respectively) and ammonia is increased (120% and 150% respectively). The applicant states that the significant increases in 4-aminobiphenyl and ammonia are expected side-effects of the genetic engineering of the VLN™(b)(4) 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 decreased, while 4-aminobiphenyl and ammonia are increased.

Regarding the appropriateness of the commercially marketed NNC cigarette comparators, there are differences in design features that may impact MSS HPHC levels and comparisons. 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 MSS 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; Song et al., 2017). 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 are only 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. The change in ventilation may also impact product use behavior (Kozlowski et al.,

1998; O'Connor et al., 2008; Stephens, 2007), which is briefly noted here given that behavioral changes can impact exposure and, therefore, user toxicities. Specifically, in describing the exposure variables and assumptions in its 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 applicant's Table 33, 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 increases and decreases can be assessed, in part, based on the carcinogenic and noncarcinogenic effects of each HPHC, the number of HPHC decreases that occur concurrently with an increase, and the magnitude and potency or effect level of the HPHCs. Qualitative evaluation of HPHC data comparisons 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 considered to be the same between the VLN™ cigarettes and the commercially marketed NNC cigarette comparators, given unknowns surrounding actual use behavior that may occur in a real-world market landscape. This may be a conservative approach, given the applicant's submission of two key studies demonstrating about a 25% reduction in product use in users that acutely and completely switch to SPECTRUM cigarettes, which are nearly identical to the VLN™ cigarettes.

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.

2.3.1.3. CI Regimen HPHC Data

The applicant did not test 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. Note that the reported 97% decrease in nicotine deliveries under the CI smoking regime supports the applicant's "95% Less Nicotine" statement for its products. Besides the substantial reported increase in ammonia, there are moderate increases in 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 is an increase in ammonia (420% and 490% respectively) as well as increases

in acrylonitrile (43% and 44% respectively) and acetaldehyde (33% and 33% respectively). The increase in ammonia is consistent with the ISO results and likely expected, as stated by the applicant, given their hypothesis around the anticipated increases in nitrogen assimilation that still occur despite genetic modification of the nicotine biosynthesis pathway.

The increases in both acrylonitrile and acetaldehyde are consistent with previous reports demonstrating that these HPHCs mainly occur in the gas phase of MSS, 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 ((b)(4) ; 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 their product compared with the average of the 6 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 cigarette may be an artifact of the number of comparator products tested. When compared with the acetaldehyde values found in the FDA50, the OS analysis of 50 popular cigarettes in 2011 through a collaboration between CTP and CDC, the percent change between the FDA50 products and the VLN™ cigarettes under the CI measurement regime is reduced to 6% less acetaldehyde in the VLN™ cigarettes compared with the FDA50. This is in line with the comparisons of the ISO regime values comparing the VLN™ cigarettes with both the 6 comparator products provided by the company, as well as with the FDA50. Therefore, the 33% higher levels of acetaldehyde found by the applicant in their comparison is not a concern.

Any assumptions pertaining to the discussion for 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 Table 3 of the toxicology review.

The toxicology review noted that increases in 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. The increase in ammonia via the ISO

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 may be offset by other HPHCs that are decreased and broadly target the respiratory tract. In this case, these increased HPHCs occur concurrently with decreases in the respiratory irritants, formaldehyde, 1,3-butadiene, and acrolein that offset the increased respiratory hazards due to 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.

2.3.1.4. Comparison Between VLN™ Cigarettes and SPECTRUM Research 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. Similar to 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 dry weight basis. 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 (100CU) 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 are different: 30% for SPECTRUM and 12.5% (target level) for VLN™ cigarettes. Behavioral and clinical pharmacology (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 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 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 MSS HPHCs, SPECTRUM NRC102 and NRC103 research cigarettes are considered similar to VLN™ King and VLN™ Menthol King cigarettes.

2.3.2. Nonclinical Studies and Literature Search

The applicant submitted information detailing a comprehensive literature search (performed by Scitek Information Services) 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.

The applicant submitted eight nonclinical studies, including one that used SPECTRUM research cigarettes and seven that used Quest cigarettes. Although Quest cigarettes, as stated by the applicant, contain VLNC tobacco, virtually every other parameter, including the tobacco blend, design features, and HPHCs are different. As such, it is unclear how the data in the seven associated studies can be extrapolated to the VLN™ cigarettes. As noted by the applicant, the only Quest-related study that may be relevant is by Ramachandran, Rubenstein, Bluestein, and Jesty (2004), which demonstrates that low nicotine cigarettes may adversely sensitize platelets to flow-induced activation compared to higher nicotine cigarettes. The direct evidence in the study of an effect on platelets pertained to nicotine: nicotine was added back to the cigarette smoke extract sample derived from zero-nicotine Quest cigarettes, which appeared to reduce the platelet-activating potential. However, this study may have several methodological issues that preclude its meaningfulness, including the lack of detail and consistency pertaining to the cigarette smoke extraction process, as well as a lack of detail, criteria and subsequent methodologies pertaining to the collection of platelets from individual test subjects and how they were used or combined during experimentation.

As stated above, 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 the qualitative discussion above that demonstrates that the potential toxicant-associated risks and hazards are likely similar.

2.3.3. Quantitative Risk Assessment (QRA)

The QRA provided by the applicant has limitations as detailed in the toxicology review; nonetheless, the conclusions generally support those of the qualitative HPHC evaluation. The toxicology review notes that the total absolute hazards and total absolute cancer risks provided by the applicant are likely inaccurate given the reasons stated below, which preclude the utility of the QRA to support the applicant's conclusions. However, PM0000491 and PM0000492 each detail HPHC comparisons of the VLN™ cigarettes to the average HPHCs of six commercially marketed conventional cigarette comparators. Across the product comparisons, regarding the ISO and CI HPHC comparisons, it is assumed, by the applicant and in the toxicology review, that the VLN™ cigarettes are used in the same manner as the commercially marketed NNC cigarette comparators. As such, any differences identified by the applicant in its QRA simply reflect the differences in HPHC levels (i.e., not impacts due to differences in CPD, puffing behavior, etc.). In

other words, the applicant applied the same exposure assumptions and the same reference toxicity values to the HPHC levels for the VLN™ cigarettes and the commercially marketed NNC cigarette comparators.

As such, the toxicology analysis focused on the HPHC yields, potencies, and magnitudes, concluding that the impact of the HPHC increases were likely not a concern, given the HPHC decreases with similar associated adverse health effects. In this case, a QRA is not necessary to quantify any potential hazard and risk differences due to the increased HPHCs in the VLN™ cigarette MSS compared to the average MSS HPHC levels of the commercially marketed NNC cigarette comparators chosen by the applicant. As noted in the HPHC evaluation, and by the applicant, the substantial reductions in TSNAs appear to be an important driver of the risk-related conclusions. Overall, from a toxicology perspective, the combined hazards and risks are likely similar, and available data may indicate that potential reductions in toxicity-related endpoints that may occur would likely be due to potential decreases in product use. As throughout this review, this conclusion is likely dependent on cigarette use behavior.

2.3.4. Summary of Toxicological Findings

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. The toxicology review provides this summary of key findings:

- The applicant cited potential evidence from nonclinical and clinical studies in support of the HPHC comparisons between VLN™ cigarettes and six commercially marketed NNC cigarettes. The results of a toxicology evaluation demonstrate that the overall toxicant-associated noncancer hazards and cancer risks due to use of VLN™ cigarettes are likely similar to the six NNC cigarettes comparators that represent approximately 25% of the cigarette market, assuming that the VLN™ cigarettes will be used in the same way as the marketed NNC cigarette comparators in this application.
- The only relevant behavior that can be extended to the toxicology review is the potential covering of filter ventilation holes as well as more intense puffing, which is available through the analysis of intense (CI regimen, ventilation holes covered) and less intense (ISO regimen, ventilation holes uncovered) MSS data. The ISO regimen HPHC data, and the associated HPHC evaluation and qualitative assessment discussed in this review, tends to support the applicant's QRA conclusions that noncancer hazards and cancer risks are likely similar or lower for users of VLN™ cigarettes compared to top market-share commercially marketed cigarettes. The CI regimen HPHC data and the associated HPHC evaluation and qualitative assessment discussed in the review likely demonstrate that the noncancer hazards and cancer risks are similar, but the applicant did not submit a separate QRA to support any risk-related conclusions based on CI regimen HPHC data. Nonetheless, the overall toxicant risk to users, assuming they completely switch to VLN™ cigarettes, is likely similar or lower than the toxicant risk for users of the six comparator cigarettes currently on the market.
- The applicant likely overestimated the potential noncancer and cancer reductions that occur in users of VLN™ King and VLN™ Menthol King cigarettes. Potential toxicant risks

for populations other than complete switchers, including dual users of VLN™ cigarettes and another tobacco product and non-users exposed to second hand smoke from VLN™ cigarettes, are likely similar as the risks to those populations posed by the six commercially marketed NNC cigarette comparators. Overall, the toxicological differences in hazards and risks between users of VLN™ cigarettes and users of the six comparators is likely impacted by anticipated changes in smoking behavior, if they occur, and not due to any inherent changes in HPHCs that, in part, arise as a result of genetic modifications that define the VLN™ tobacco. Tobacco filler and other material ingredients in the VLN™ cigarettes are, overall, likely similar to those in the six comparators, and any related impact due to their combustion, (i.e., HPHC production) are unlikely to raise toxicology concerns. Specifically, these ingredients likely do not raise additional concerns, given the relative reduction in HPHCs that may have similar adverse health effects to any increased ingredients potentially entering the MSS unchanged by combustion. Thus, overall, if there were evidence to support that users would switch to the VLN™ cigarettes, then toxicant-related health risks are likely to be similar to those due to the use of the six comparators. If switching resulted in reductions in CPD, then use of VLN™ cigarettes may result in lower toxicant exposure or health risks in comparison to those due to the use of the six comparators.

- In addition, evidence from clinical studies may indicate that the associated noncancer hazards and cancer risks could be lower compared to the six NNC cigarette comparators, as users of products very similar (i.e., SPECTRUM VLNC cigarettes) to the VLN™ cigarettes tend to decrease their CPD and puffing volumes if they completely and acutely switch from their UB-NNC cigarettes to very low nicotine cigarettes. This suggests that toxicological impacts may be proportionately decreased if users were to switch, due to a reduction in CPD. To this latter point, clinical biomarkers of exposure (e.g., NNAL, CO, PheT, and 3-HMPA) tend to support that acute and complete switching is associated with HPHC and CPD reductions, whereas gradual switching is not, suggesting that the reduction in HPHCs, and therefore associated hazards or risks, likely occurs via the reduction in CPD.
- Noncancer hazards and cancer risks to dual users of tobacco products, where at least one product is VLN™ King or VLN™ Menthol King cigarettes, are also likely to be similar or lower than hazards and risks to NNC cigarette smokers, to the extent that the use of such additional tobacco products, or NRT, is less harmful than the six comparators. By extension of the comparative risks for complete switchers, or for dual users in which one product is one of the VLN™ cigarettes, the associated exposures and risks posed to non-users through second hand smoke (SHS) are also likely similar to exposure to SHS from NNC cigarettes. The extent to which this is true for dual users is, however, also dependent on the likelihood that the use of additional tobacco products is less harmful than use of the six comparators. Using VLN™ cigarettes compared to quitting tobacco use or switching to NRT would increase harm, as toxicant exposures would be similar to exposures resulting from NNC cigarette use. The likelihood that users of VLN™ cigarettes switch to NRT or relapse back to VLN™ cigarettes is outside the scope of this review. For non-users seeking to initiate smoking by using VLN™ cigarettes, their toxicant exposures and risks would likely be similar to those of naïve users who initiate smoking with an

NNC cigarette such as the six comparators.

- Overall, if there were evidence to support that users would switch to the VLN™ cigarettes, then toxicant health risks are likely to be similar to those of the six comparators that represent 25% of the cigarette market. If switching resulted in reductions in CPD, then use may result in lower toxicant or health risks in comparison to use of the six comparators. Given these conclusions, from the toxicology perspective, the information presented in the applications does not raise concerns about issuing marketing orders.

As TPL, I agree with the toxicology review conclusion. 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. However, the potential for a relative benefit compared to NNC cigarettes exists for smokers who switch completely to VLN™ cigarettes, then reduce cigarette use, and eventually totally quit.

2.4. Individual Health Impact

2.4.1. Overview of Behavioral and Clinical Pharmacology (BCP) Studies

The applicant originally submitted two completed abuse liability studies on VLN™ cigarettes as well as a literature review that allowed for an assessment of BCP outcomes. Amendment PM0000519 contained a third clinical study, a 6-week switching study, sponsored by the applicant that was also considered as part of the FDA scientific evaluation.

The applicant's studies on VLN™ cigarettes provided information on VLN™ King and VLN™ Menthol King cigarette abuse liability, including evaluations of subjective effects using visual analog scales (VAS), pharmacokinetics (PK), and product use behaviors (e.g., amount of product consumed, topography).

The two abuse liability studies and one 6-week switching study were:

1. NCT0359751: Evaluation of the Abuse Liability of Very Low Nicotine Cigarettes
2. NCT03559725: Evaluation of the Abuse Liability of Very Low Nicotine Mentholated Cigarettes
3. NCT03571724: A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes

The first two studies evaluating abuse liability (NCT0359751 and NCT03559725) were designed in the same way but used different study products. A general summary of study design is as follows:

Study products: VLN™ King cigarettes, UB-NNC cigarettes, 4 mg Nicorette® Original Flavor nicotine gum and VLN™ Menthol King cigarettes, UB-NNC menthol cigarettes, 4

mg Nicorette® White Ice Mint™ nicotine gum. The VLN™ cigarettes and nicotine gums were provided free of charge; participants supplied their UB-NNC cigarettes in both studies.

Study design: Six-day, within-subject, confined, cross-over study. Phase A (Days 1-3) involved four-hour ad libitum use of one of the three study products. Phase B (Days 4-6) consisted of controlled use (10 puffs, 3 seconds per puff, 30 second interpuff interval; chew and park method for 10 minutes), followed by ad libitum use of the same product for 10 minutes.

Relevant study outcomes: Phase A outcome measures included a self-reported VAS to assess "use product again" at the end of the session and product use behaviors (number of units consumed, time spent per unit). Phase B outcome measures included nicotine PK parameters (i.e., C_{max} (maximum measured plasma nicotine concentration), T_{max} (time of the maximum measured plasma nicotine concentration), $T_{1/2}$ (apparent first-order terminal nicotine elimination half-life calculated as $0.693/K_{el}$ of the plasma concentration-time curve from time 0 to 180 minutes), AUC_{0-180} (area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time 0 to 180 minutes), VAS Tobacco/Nicotine Withdrawal Scale, VAS Direct Effects of Product Questionnaire, and topography (i.e., number of puffs, puff duration).

A general summary of the third study evaluating BOE after 6 weeks of exposure (NCT03571724) is as follows:

Study products: VLN™ King and Menthol King Cigarettes, participant's UB-NNC cigarettes. VLN™ King and Menthol King cigarettes were provided free of charge at each visit; participants purchased their own UB-NNC cigarettes.

Study design: An open-label, randomized, forced-switching study conducted at two United States study sites. All participants smoked their UB-NNC cigarettes for one week, then were randomized to either continue smoking their UB-NNC cigarettes (n=22 non-menthol, n=20 menthol) or switch to smoking VLN™ King (n=50) or VLN™ Menthol King (n=50) cigarettes for 6 weeks. A subset of 18 non-menthol and 18 menthol smokers assigned to switch to smoking VLN™ cigarettes completed the topography assessments. A further subset of 12 non-menthol and 12 menthol smokers who completed the topography assessments also completed a nicotine PK assessment. Participants were confined overnight to collect 24-hour urine samples for BOE assessments and for nicotine PK and topography assessments in the selected participants. Measures were collected at the end of Week -1 (baseline), Week 2, Week 4 (subjective questionnaires only), and Week 6.

The applicant analyzed the data based on a per protocol (PP) population (i.e., participants who were near complaint based on if their ratio of [plasma cotinine/CPD VLN]/[plasma cotinine/CPD baseline] exceeded 0.2; n=10 non-menthol, n=9 menthol) and an intent-to-treat (ITT) population (i.e., participants who had at least one valid

recording of cigarette consumption, with documented non-compliance; n=43 non-menthol, n=42 menthol). The rationale for this analysis was to present the best possible outcome of completely switching to VLN™ cigarettes (PP population) and the more likely situation, where consumers who want to quit may have difficulty adhering to just smoking VLN™ cigarettes and would alternate between UB-NNC cigarettes and VLN™ cigarettes (ITT population).

Relevant study outcomes: The primary study outcomes were CPD, number of collected cigarette butts to measure compliance and accuracy of self-report, and puff topography (puff duration, puff volume, peak puff flow rate, average flow rate and inter-puff interval). Secondary outcomes included changes in BOE (urinary NNAL [an NNK biomarker], NNN, 3-hydroxypropylmercapturic acid [3-HPMA, an acrolein biomarker], S-phenylmercapturic acid [S-PMA , a benzene biomarker], 1-hydroxypyrene [1-HOP, hydroxypyrene biomarker], TNE, blood carboxyhemoglobin [COHb], plasma cotinine), nicotine PK (C_{max}, T_{max}, AUC), and subjective measures of dependence (Fagerström Test for Cigarette Dependence [FTCD]), smoking urges (Brief Questionnaire of Smoking Urges [QSU-Brief]), and withdrawal symptoms (Minnesota Nicotine Withdrawal Scale - Revised [MNWS-R]).

Results of these three studies, as well as relevant findings from the literature, are discussed by outcome below.

2.4.2. Nicotine Pharmacokinetics

Abuse Liability Studies NCT0359751 and NCT03559725:

During the controlled use portion of Phase B of the studies, the nicotine C_{max} for VLN™ King cigarettes and VLN™ Menthol King cigarettes was significantly lower (0.47 ng/ml and 0.40 ng/ml at 7 minutes, respectively) than UB-NNC cigarettes (13.7 ng/ml at 7 minutes) ($p < 0.0001$) and Nicorette® Original Flavor or Nicorette® White Ice Mint™ nicotine gum (3.5 ng/ml and 3.1 ng/ml at 20 minutes respectively) ($p < 0.0001$). There were no differences in nicotine T_{max} between VLN™ King cigarettes and UB-NNC cigarettes or between VLN™ Menthol King and UB-NNC cigarettes. The plasma nicotine AUC_{0-180} for VLN™ King cigarettes was significantly lower (26.2 ng*min/ml) than UB-NNC (770.8 ng*min/ml) ($p < 0.0001$) and nicotine gum (342.8 ng*min/ml) ($p < 0.0001$). The plasma nicotine AUC_{0-180} for VLN™ Menthol King cigarettes was also significantly lower (30.4 ng*min/ml) than UB-NNC (932.0 ng*min/ml) ($p < 0.0001$) and nicotine gum (359.3 ng*min/ml) ($p < 0.0001$). There were no statistically significant differences in nicotine $T_{1/2}$ (controlled use) for any of the product comparisons in the VLN™ King cigarettes study. However, nicotine $T_{1/2}$ was significantly shorter for the VLN™ Menthol King cigarettes compared with UB-NNC cigarettes (median difference = -67.7, 95% CI = -94.3, -12.3) and nicotine gum (median difference = - 68.0, 95% CI = -98.4, -13.8); a smaller sample size for VLN™ Menthol King cigarettes may have influenced these results; however, any potential differences in nicotine $T_{1/2}$ did not appear to translate to differences in UB-NNC cigarette and VLN™ Menthol King cigarette use behavior or topography.

During the ad libitum portion of Phase B of the studies, the nicotine C_{max} for VLN™ King cigarettes and VLN™ Menthol King cigarettes was significantly lower (0.57 ng/ml and 0.53 ng/ml at 7 minutes, respectively) than UB-NNC cigarettes (16.97 ng/ml and 19.2 ng/ml at 7 minutes, respectively) ($p < 0.0001$) and Nicorette® Original Flavor or Nicorette® White Ice Mint™ nicotine gum (3.2 ng/ml and 2.0 ng/ml at 20 minutes, respectively) ($p < 0.0001$). There were no differences in nicotine T_{max} between VLN™ King cigarettes or VLN™ Menthol King cigarettes and UB-NNC cigarettes. The plasma nicotine AUC_{0-180} for VLN™ King cigarettes was significantly lower (28.3 ng*min/ml) than UB-NNC cigarettes (879.75 ng*min/ml) ($p < 0.0001$) and nicotine gum (277.3 ng*min/ml) ($p < 0.0001$). Similarly, the plasma nicotine AUC_{0-180} for VLN™ Menthol King cigarettes was also significantly lower (33.5 ng*min/ml) than UB-NNC cigarettes (1035.3 ng*min/ml) ($p < 0.0001$) and nicotine gum (231.7 ng*min/ml) ($p < 0.0001$). Furthermore, nicotine $T_{1/2}$ was significantly shorter for the VLN™ King cigarette compared with UB-NNC cigarettes (median difference = -25.3, 95% CI = -41.3, -4.8) and nicotine gum (median difference = - 41.4, 95% CI = -68.0, -12.1). The nicotine $T_{1/2}$ was also significantly shorter for the VLN™ Menthol King cigarettes (median difference = - 25.2, 95% CI = -73.0, -21.3) and UB-NNC cigarettes (median difference = 21.3, 95% CI = -3.7, 48.4) compared to nicotine gum. For both studies, a smaller sample size and large variability for the VLN™ cigarettes may have influenced these results; however, any potential differences in nicotine $T_{1/2}$ did not appear to translate to differences in UB-NNC cigarette and VLN™ cigarette use behavior or topography.

The total nicotine exposure and maximum level of nicotine in the blood was significantly lower for the VLN™ cigarettes in both studies compared with the UB-NNC cigarettes and the nicotine gum. The time it took to reach the maximum nicotine concentration in the blood was equivalent between the VLN™ cigarettes and UB-NNC cigarettes in each study, as expected when comparing two cigarette products delivering nicotine. The PK profile of both the VLN™ cigarettes indicates a lower abuse liability than their UB-NNC cigarette comparator.

The 6 week Switching Study NCT03571724:

Nicotine PK assessments indicated that for both VLN™ King and Menthol King cigarettes, the C_{max} and AUC were significantly reduced from baseline UB-NNC cigarette smoking by ≥ 97% at Weeks 2 and 6 of the study (% reduction for these comparisons ranged from 96.9 – 99.0, all p-values <0.0001). Nicotine T_{max} values following use of VLN™ cigarettes were comparable to UB-NNC cigarettes.

2.4.3. Behavioral Pharmacology

2.4.3.1. Abuse Liability

The applicant provided a literature review of published acute laboratory studies that assessed nicotine abuse liability outcomes in participants using SPECTRUM or other VLNC cigarettes that are substantially similar to VLN™ cigarettes, but not exactly the same (i.e., Quest, Ultratech). A study in young adults (ages 18-25 years) showed that SPECTRUM non-menthol VLNC cigarettes are associated with reduced plasma nicotine levels compared to UB-NNC cigarettes, and these differences are not dependent upon differences in nicotine metabolism or sex (Faulkner et al., 2017; Faulkner et al., 2018). Studies utilizing other VLNC cigarettes consistently support

significantly reduced levels of plasma nicotine in participants after ad libitum menthol and non-menthol VLNC cigarette use compared to UB-NNC and NNC cigarettes (Cobb, Weaver, & Eissenberg, 2010; Pickworth, Nelson, Rohrer, Fant, & Henningfield, 1999; Rose & Behm, 2004).

Self-reported subjective effects (e.g., drug “liking,” “satisfaction”) are widely used measures of reinforcing efficacy and abuse liability for drugs and tobacco products. Drug “liking” is associated with drug self-administration and has been shown to be the most sensitive and reliable subjective effects measure of abuse liability (Carter & Griffiths, 2009). Several studies compared the subjective effects of VLNC, NNC, or UB-NNC cigarettes using self-reported measures of drug effects (e.g., Cigarette Evaluation Scale, Smoking Effects Questionnaire, VAS items). Studies typically found that VLNC cigarettes were associated with lower subjective effects ratings compared to UB-NNC and NNC cigarettes. None of the studies reviewed found that VLNC cigarettes were associated with greater subjective appeal compared to UB-NNC or NNC cigarettes.

In acute laboratory exposure conditions, several studies found that VLNC cigarettes were rated lower in cigarette “liking” compared to NNC cigarettes (Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013; Lindsey et al., 2013; Perkins, Karelitz, & Kunkle, 2017, 2018; Rose & Behm, 2004; Schlagintweit & Barrett, 2016). However, other studies found no significant differences in “liking” as a function of nicotine content in cigarettes (Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Juliano, Donny, Houtsmuller, & Stitzer, 2006). Other subjective effects (e.g., “good” or “positive” effects; “bad” or “negative” effects) co-vary with drug “liking.” On average, VLNC cigarettes were rated lower on other positive subjective effects items (e.g., “satisfaction,” “pleasure,” “taste,” “strength,” “stimulation”) compared to NNC cigarettes (Hatsukami, Heishman, et al., 2013; Juliano, Fucito, & Harrell, 2011; Macqueen et al., 2012; Perkins et al., 2017, 2018) and UB-NNC cigarettes (Cobb et al., 2010). VLNC cigarettes were also rated lower on “dizziness,” likely due to the low nicotine content in these products (Juliano et al., 2011), and higher on items such as “dislike” and “unpleasant” compared to UB-NNC or NNC cigarettes (Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013).

Several studies assessed subjective effects of VLNC cigarettes following extended exposure, typically over the course of several weeks. Findings from these studies were relatively similar to findings from brief exposure studies. On average, VLNC cigarettes were rated as less appealing (e.g., lower ratings of “liking,” “satisfaction,” “pleasure”) compared to NNC cigarettes (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Mercincavage et al., 2016). However, at least one study found no differences in subjective effects as a function of nicotine content in cigarettes (Benowitz et al., 2012). Positive subjective effects ratings for VLNC cigarettes were shown to remain constant or decrease over time (Buchhalter et al., 2005; Walker et al., 2012).

Donny and colleagues (2007) conducted a study that examined the effects of Quest VLNC cigarettes on subjective effects in smokers who were confined to a residential research facility throughout the study, thereby permitting an assessment of appeal under conditions of complete substitution. During 11 days of exposure to study cigarettes, participants assigned to the VLNC cigarette group rated positive subjective effects of cigarettes (e.g., "enjoyable") lower and negative subjective effects (e.g., "unpleasant") higher than baseline subjective effects of UB-NNC cigarettes. Similarly, during the first few days of exposure to study cigarettes,

participants who received NNC cigarettes rated positive subjective effects of cigarettes lower and negative subjective effects higher than baseline subjective effects of UB-NNC cigarettes; however, these effects dissipated over time such that subjective ratings of NNC cigarettes were similar to UB-NNC cigarettes by the end of the study (Donny et al., 2007).

BCP also identified two studies that assessed the effects of menthol on SPECTRUM VLNC cigarette perceptions. Perkins and colleagues (2018) investigated the effects of menthol on subjective and behavioral responses to VLNC cigarettes in 73 adult smokers. Subjective effects were measured after smoking each of five cigarettes. A main effect of menthol on subjective effects was observed; however, no significant interaction effect of nicotine content and menthol on subjective effects was observed. Participants chose significantly more puffs from NNC menthol cigarettes than VLNC menthol cigarettes, with no significant differences due to menthol or due to interactions between menthol and nicotine content. Greater differences in subjective effects between menthol NNC and VLNC cigarettes predicted choice for NNC cigarettes regardless of menthol content. Additionally, Hatsukami and colleagues (2013) assessed menthol's influence on the subjective effects of three SPECTRUM cigarettes (i.e., 0.4 mg nicotine/g, 5.7-5.8 mg/g, 11.4-12.8 mg/g) in 51 adult smokers. Regardless of nicotine content, VLNC non-menthol cigarette smokers rated the study cigarettes as having significantly higher positive subjective effects ratings (e.g., "satisfying," "pleasing," "liked") than VLNC menthol cigarette smokers. VLNC non-menthol cigarettes were also associated with greater craving reduction than the menthol cigarettes; however, there was no interaction between nicotine content and menthol status. These findings suggest that VLNC menthol cigarettes have reduced positive subjective effect ratings compared to NNC menthol cigarettes and smokers are more likely to choose NNC menthol cigarettes compared to VLNC menthol cigarettes.

2.4.3.2. Use Behavior and Topography

The applicant-submitted abuse liability studies compared acute smoking topography (number of puffs, puff duration) of VLN™ King and VLN™ Menthol King cigarettes to UB-NNC cigarettes and showed that participants had similar puff durations; however, smokers took fewer puffs of the VLN™ cigarettes than UB-NNC cigarettes. The majority of studies in the applicant-submitted literature review support these findings; 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.

In the applicant-submitted 6-week switching study assessment of smoking topography during 1-hour ad libitum sessions found that participants in both the VLN™ King and Menthol King cigarette groups significantly differed in some topography measures from their UB-NNC cigarette smoking (recorded at baseline), including shorter total puff durations, smaller total puff volumes, shorter inter-puff intervals, and decreased average number of puffs.

The applicant also provided a summary of smoking topography assessments from the VLNC cigarette literature. Single session studies suggest that participants may alter their smoking topography when smoking VLNC cigarettes compared to UB-NNC cigarettes; however, these use behaviors generally do not lead to an increase in exposure to nicotine or other HPHCs. Single session studies have found that smokers may increase puff duration and decrease the time between puffs when smoking VLNC cigarettes, but generally take fewer puffs from the cigarette, resulting in decreased total puff volume (e.g., Hammond & O'Connor, 2014; Higgins et al., 2017; Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007; Tidey, Cassidy, & Miller, 2016). Although some smokers may partially compensate when smoking VLNC cigarettes (e.g., Kassel et al., 2007; Macqueen et al., 2012), this effect was present during initial cigarette exposures and diminished as participants smoked more cigarettes during single sessions (Macqueen et al., 2012). CO boost has also been examined to determine if compensatory smoking occurs with smoking VLNC cigarettes. Single session studies find no significant difference in CO boost between VLNC and NNC cigarettes, supporting that any differences in topography from smoking VLNC cigarettes do not lead to increased exposure (e.g., Juliano et al., 2011; Rose & Behm, 2004; Strasser et al., 2007). Longer-term studies (i.e., five or more days) also do not find significant differences in smoking topography or CO boost between smokers of VLNC and NNC cigarettes, supporting that any compensatory smoking associated with smoking VLNC cigarettes is transient and does not significantly affect exposure (e.g., Donny et al., 2015; Donny & Jones, 2009; Hatsukami, Heishman, et al., 2013; Hatsukami et al., 2018; Mercincavage et al., 2016; Vogel et al., 2014).

The BCP review identified one study that assessed whether menthol moderated the effects of VLNC cigarettes on smoking topography (Davis et al., 2019). Smoking topography measures (i.e., puff volume, puff duration, interpuff interval, puff number, flow rate) were assessed in a total of 169 participants (36% menthol smokers) from three vulnerable populations (i.e., low socioeconomic status women, opioid maintained adults, adults with mental illness) after participants smoked each of four SPECTRUM research cigarettes (15.8, 5.2, 2.4, 0.4 mg/g) in an ad libitum manner. There were significant main effects of dose on puff volume, puff number, and flow rate, with higher nicotine doses associated with increased exposure. Menthol status did not moderate the effect of dose on these measures, suggesting that menthol would not differentially alter smoking topography in VLN™ cigarette smokers.

Overall, findings indicate that, in general, individuals who smoke VLNC cigarettes demonstrate no significant differences in smoking topography relative to those who smoke UB-NNC or NNC cigarettes. Any observed differences in smoking topography measures are associated with reductions in tobacco smoke exposure (e.g., lower total puff volume).

2.4.3.3. Product Use/Consumption

The applicant-submitted abuse liability studies included 4-hour ad libitum use sessions, one for each of the three study products on separate days. In these ad libitum sessions product use behaviors such as number of units consumed and time spent per unit were recorded. They found that participants consumed slightly more VLN™ King cigarettes (M(SD) = 8.2 ± 4.3 vs. 7.8

± 2.6) than UB-NNC cigarettes, but smoked VLN™ King cigarettes for less time (M(SD) = 4.7 ± 1.7 vs. 6.0 ± 2.1 minutes). Similarly, they found that participants consumed slightly more VLN™ Menthol King cigarettes (M(SD) = 6.8 ± 3.4 vs. 6.2 ± 1.9) than UB-NNC cigarettes, but smoked VLN™ Menthol King cigarettes for less time (M(SD) = 5.1 ± 2.4 vs. 6.3 ± 2.3 minutes). Overall, use behavior was similar for the study cigarettes and UB-NNC cigarette in both studies.

The applicant submitted 6-week switching study found that, although there was an initial increase in mean CPD from baseline in Week 1 in VLN™ King cigarette smokers (17.94 to 20.02 CPD), mean CPD was decreased from Week 3 to Week 6 in these smokers (16.84 to 15.13 CPD); however, the decreased CPD in VLN™ King cigarette smokers was not significantly different from baseline at any time point assessed in the study. In contrast, VLN™ Menthol King cigarette smokers significantly decreased CPD from baseline across the 6-week study period (Baseline-14.75 to Week 6- 11.37 CPD). Of note, combined VLN™ cigarette data showed a significant reduction in CPD from baseline to Week 6. Regarding non-compliance, ITT participants reported smoking less than one non-study CPD during the study. Cigarette butt collection confirmed the findings on self-reported CPD and study compliance.

The applicant also provided a summary of published studies ranging from six weeks to 20 weeks that evaluated CPD in participants who switched to smoking VLNC cigarettes. Both gradual and immediate reduction studies were included; given that the immediate reduction studies provide the most comparable situation to how VLN™ cigarettes would be introduced to the market, these studies hold the greatest weight.

Some studies evaluating VLNC cigarette smoking over the course of six weeks to 20 weeks found that, compared to baseline, overall CPD is significantly reduced in participants who immediately switched to VLNC cigarettes. The largest study to date on VLNC cigarettes was conducted over 20 weeks. Despite high rates of non-compliance in smoking non-study cigarettes, there was an overall reduction in total CPD in smokers who switched to smoking VLNC cigarettes. Hatsukami et al. (2017) also conducted a study examining CPD and alternate tobacco product use following concurrent use of low nicotine content (LNC) cigarettes with non-cigarette combusted products, non-combusted products, and/or other nicotine-containing products. The study found that participants in LNC cigarette groups smoked fewer CPD overall and reported less combusted product use than those in the NNC cigarette group. LNC cigarette smokers reported higher use of alternative nicotine-containing products compared to NNC cigarette smokers, with ENDS being the highest reported dually used product.

However, other studies of immediate reduction did not find a significant difference in CPD. Walker et al. evaluated participants (n=60) who smoked either their UB-NNC or VLNC cigarettes (Magic; 0.04 mg nicotine yield) for 12 weeks. While there was a reduction in CPD from baseline to six weeks in VLNC cigarette smokers compared to UB-NNC cigarette smokers, the change from baseline to 12 weeks was not significant. As a result, overall, participants in the VLNC cigarette group smoked a comparable amount of CPD as participants in the UB-NNC cigarette groups over the 12-week period; participants in the VLNC cigarette group replaced some of their UB-NNC cigarettes with VLNC cigarettes (Walker et al., 2015). Donny and Jones also did not find that VLNC cigarette smokers (n=68) reduced their CPD over a shorter time period (nine

days); however, VLNC cigarette smokers who also used nicotine patches did reduce their CPD compared to NNC cigarette smokers. One 5-day study of participants (n=31) confined to a hotel monitored the effects of exclusive smoking of VLNC cigarettes and noted an increase in CPD while at the hotel compared to baseline UB-NNC cigarette smoking (Denlinger et al., 2016); however, this effect was likely due to participants receiving free cigarettes while being confined to a hotel for five days. Despite the increase in CPD, total nicotine equivalent (TNE) levels were reduced by 92% compared to UB-NNC cigarette smoking.

Regarding the role of menthol on CPD, evidence extrapolated from published studies of NNC menthol cigarettes does not suggest that menthol increases the number of CPD compared to non-menthol NNC cigarettes (Section 2.4.4.). Therefore, combined data on menthol and non-menthol VLNC cigarettes can be extrapolated to VLN™ King Menthol cigarettes. One study submitted by the applicant conducted a subgroup analysis and found an overall significant reduction in CPD in smokers who switched from UB-NNC cigarette, with no significant interactions with menthol for total CPD (Donny et al., 2015). A 2019 Society for Research on Nicotine and Tobacco (SRNT) presentation that conducted a secondary analysis of the 20-week Hatsukami study (2018) for effects of menthol on trial outcomes also found that menthol smokers who switched from UB-NNC to VLNC cigarettes reduced their overall CPD, though reductions in CPD were to a lesser extent than non-menthol VLNC smokers (Delinger, 2019).

Overall, these data suggest that smoking VLNC cigarettes may lead to an overall reduction in CPD compared to smoking UB-NNC cigarettes. Some consumers, in particular those who dual use VLNC and UB-NNC cigarettes, may not decrease their overall cigarette consumption; however, dual use of other nicotine-containing products, such as NRT or ENDS, may aid in reducing CPD (Donny & Jones, 2009; Hatsukami, Hertsgaard, et al., 2013; Hatsukami et al., 2017). While one study found that some smokers increase CPD while using VLNC cigarettes, this effect is unlikely to be related to VLNC cigarettes themselves, but rather an effect of being confined to an environment with free cigarettes for several days.

2.4.3.4. Craving, Withdrawal, and Dependence

The applicant submitted 6-week switching study assessed subjective measures of dependence (FTCD), smoking urges (QSU-Brief), and withdrawal symptoms (MNWS-R). Results of the FTCD score comparison indicated that VLN™ King cigarette smokers had significantly higher dependence scores at Week 2 compared to baseline, though this effect subsided during the study, as there was no significant difference in FTCD score from baseline at Week 6. FTCD scores were significantly reduced in VLN™ Menthol King cigarette smokers at Week 6 compared to baseline. QSU-Brief results at Week 2 indicated that VLN™ King cigarette smokers experienced a greater urge to smoke and less anticipated relief from withdrawal compared to baseline; however, these effects were not significant at Week 6. In VLN™ Menthol King cigarette smokers, QSU-Brief scores indicated that urge to smoke was marginally decreased (p= 0.06) and anticipated relief from withdrawal was significantly reduced from baseline at Week 6. Mean MNWS-R score in VLN™ King cigarette smokers was significantly higher at Week 2 compared to baseline, indicating greater withdrawal symptoms, but did not significantly differ from baseline by Week 6. In VLN™ Menthol King cigarette smokers, mean MNWS-R score was

marginally decreased from baseline at Week 6 (p=0.05); this reduction in mean MNWS-R score was significant in UB-NNC menthol smokers at Week 6 compared to baseline (p=0.005). Of note, combined VLN™ King and Menthol King cigarette data at Week 6 did not detect a significant difference in FTCD, QSU-Brief, or MNWS-R score compared to baseline.

The applicant provided a literature review of published acute laboratory studies that assessed nicotine/tobacco craving and withdrawal in participants using SPECTRUM or other VLNC cigarettes, which are substantially similar to VLN™ King and VLN™ Menthol King cigarettes but not exactly the same (i.e., Quest, Ultratech). Nicotine produces a characteristic withdrawal syndrome manifested by irritability, anxiety, depressed mood, difficulty concentrating, increased appetite, insomnia, and restlessness. Although craving is often characterized as a symptom of nicotine withdrawal, it can occur in the absence of other withdrawal symptoms. Thus, craving is usually measured and reported separately from withdrawal. Due to their lower nicotine content, VLNC cigarettes might be expected to increase craving and withdrawal relative to UB-NNC or NNC cigarettes. Study results suggest that while VLNC cigarettes may be associated with increased withdrawal compared to UB-NNC or NNC cigarettes, these effects appear to be transient and usually dissipate after the first week of use. VLNC cigarettes do not appear to be associated with sustained increases in cigarette craving compared to NNC cigarettes.

In acute exposure laboratory studies, VLNC cigarettes initially suppressed craving and withdrawal symptoms relative to baseline measures that were typically assessed following overnight abstinence (Addicott et al., 2014; Barrett, 2010; Barrett & Darredeau, 2012; Tidey et al., 2013). This is likely due to the conditioned reinforcing effects of sensorimotor stimuli that are repeatedly paired with nicotine through the process of smoking, resulting in these stimuli being able to acutely ameliorate nicotine craving and withdrawal. Many studies showed that VLNC cigarettes can reduce craving and withdrawal to a similar degree as UB-NNC or NNC cigarettes (Cobb et al., 2010; Eid, Fant, Moolchan, & Pickworth, 2005; Higgins et al., 2017; Juliano et al., 2006; Perkins & Karelitz, 2015). However, some studies observed that suppression of craving and withdrawal symptoms was lower after smoking VLNC cigarettes than UB-NNC or NNC cigarettes (Hatsukami, Heishman, et al., 2013; Juliano et al., 2011). Notably, some of these brief exposure studies reported gender differences and generally found that female smokers experienced greater reductions in craving (Barrett & Darredeau, 2012; Hatsukami, Heishman, et al., 2013) or withdrawal (Barrett, 2010; Perkins & Karelitz, 2015) compared to male smokers after smoking VLNC cigarettes.

During extended exposure, VLNC cigarettes tend to increase withdrawal symptoms during the initial week after switching; however, these differences do not persist (Donny & Jones, 2009; Hatsukami et al., 2010; Hatsukami et al., 2018). One study found that, after switching to VLNC cigarettes from UB-NNC cigarettes for one week, withdrawal symptoms increased with no reported change in craving. However, these effects were relatively brief, and within six weeks, withdrawal symptoms returned to baseline levels and craving steadily decreased below baseline levels. Another study demonstrated that six weeks of VLNC cigarette exposure resulted in less craving and no difference in other withdrawal symptoms compared to NNC cigarettes (Donny et al., 2015). A 20-week study showed higher withdrawal scores at Week 1 among those

switching to VLNC cigarettes compared to NNC cigarettes; however, these differences dissipated after the first week (Hatsukami et al., 2018). Craving scores were generally lower among those switching to VLNC cigarettes compared to NNC cigarettes.

Craving and withdrawal symptoms were also assessed in several smoking cessation studies where participants were provided VLNC cigarettes along with pharmacotherapy (e.g., NRT, varenicline). One study showed that VLNC cigarettes plus NRT can produce persistent reductions in craving after three and six weeks of exposure (Walker et al., 2012). Another study provided participants with NNC or VLNC cigarettes plus a nicotine patch prior to a quit date. Those who received VLNC cigarettes and patches experienced less frequent and less intense cravings, as well as similar withdrawal symptoms before and after the quit date, compared to those who received NNC cigarettes before the quit date (Rezaishiraz, Hyland, Mahoney, O'Connor, & Cummings, 2007). Another study found that VLNC cigarettes plus either varenicline or NRT resulted in decreased craving compared to pharmacotherapy alone, with no differences in withdrawal across groups (McRobbie, Przulj, Smith, & Cornwall, 2016).

Davis and colleagues (2019) assessed whether menthol status moderated the effects of VLNC cigarettes on withdrawal and craving. Each of the nicotine doses (15.8, 5.2, 2.4, 0.4 mg/g) reduced craving and withdrawal scores from baseline, and menthol status did not moderate the effect of dose on these measures. These findings suggest that VLN™ cigarettes would be associated with similar acute relief of craving and withdrawal in menthol and non-menthol smokers.

The applicant also discussed studies from its literature review assessing dependence. Over the course of regular use, cigarette smoking can lead to symptoms of nicotine dependence, which may include tolerance to nicotine's effects, withdrawal upon cessation of use, craving, and unsuccessful efforts to quit smoking. Because dependence takes time to develop or change, it is often measured under conditions of extended exposure. Studies typically assess dependence with the Fagerström Test for Nicotine Dependence (FTND), FTCD, Nicotine Dependence Syndrome Scale (NDSS), and Wisconsin Inventory of Smoking Dependence Motives (WISDM). There is consistent evidence suggesting that switching to VLNC cigarettes for an extended duration of time is associated with decreased dependence scores among smokers interested and not interested in quitting. These findings support the applicant's conclusions that using VLNC cigarettes reduce nicotine exposure and, therefore, may reduce nicotine dependence.

Several studies gradually stepped down the nicotine content of cigarettes over the course of weeks or months. In a study that used Quest cigarettes to step down nicotine content weekly over the course of four weeks, there were no differences in overall dependence scores as a function of the cigarette's nicotine content. Because not all study cigarettes were VLNC cigarettes, these products were only used for one week, and this short duration may have been insufficient to allow for observable changes in dependence (Hammond & O'Connor, 2014). Another study in 135 participants who smoked either gradually reduced nicotine content cigarettes (12mg to 1 mg, reduced monthly) or UB-NNC cigarettes over the course of six months found no difference in dependence when comparing data from baseline to week 26. However, when comparing only data from Week 14 to Week 26, when participants were primarily

smoking VLNC cigarettes, there was a significant decrease in dependence in participants who received gradually reduced nicotine content cigarettes (Benowitz et al., 2012). In a follow-up study, participants who received gradually reduced nicotine content cigarettes were given VLNC cigarettes for an additional six months (Benowitz et al., 2015), and dependence scores significantly decreased between baseline and 18 months.

Immediate nicotine reduction from UB-NNC cigarettes to VLNC cigarettes consistently reduced dependence scores compared to those who smoked NNC or UB-NNC cigarettes for six (Donny et al., 2015), 12 (Walker et al., 2015), and 20 weeks (Hatsukami et al., 2018) in participants not interested in quitting smoking. In a smoking cessation study where participants endorsed wanting to quit, VLNC cigarettes were also associated with reductions in nicotine dependence at six weeks compared to baseline (Hatsukami et al., 2010). Finally, in a study that examined the effects of VLNC cigarettes on latency to smoke in smokers inhabiting a residential research facility, time to first cigarette, a strong predictor of dependence, was significantly longer among smokers who only had access to VLNC cigarettes for 11 days compared to those who only had access to NNC cigarettes (Donny et al., 2007).

2.4.3.5. Cessation

The applicant's clinical studies on VLNC cigarettes evaluated the effect of smoking VLNC cigarettes on cessation. The X-22 VLNC cigarette was menthol flavored, while the Quest cigarette was non-menthol. These studies, in addition to the literature, were extrapolated to VLN™ Menthol King and VLN™ King cigarettes, respectively, to address the likelihood of improved cessation outcomes. One study of smokers motivated to quit found that, at four weeks, participants who smoked VLNC cigarettes and received NRT were more likely to be abstinent than those who smoked VLNC cigarettes alone or NNC cigarette with the patch. Neither study found a significant difference in longer-term quit rates (i.e., three- and six-month follow-up) compared to NNC cigarette smokers. Studies from the literature found that among smokers motivated to quit, VLNC cigarettes may facilitate abstinence due to reduced nicotine exposure. 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 NNC cigarette smokers; however, quit attempts were greater in VLNC cigarette smokers.

In addition, several extended duration VLNC studies in the literature assessed self-reported quit attempts as a secondary study aim. While one study showed no significant differences in quit rates among nondaily smokers who used VLNC or NNC cigarettes for 10 weeks (Shiffman, Kurland, Scholl, & Mao, 2018), other studies showed that participants who smoked VLNC cigarettes were more likely to report a quit attempt after six weeks (Donny et al., 2015) and had a greater number of cigarette-free days after 18 weeks (Hatsukami et al., 2018) compared to those who smoked NNC cigarettes.

These findings suggest that VLN™ cigarettes may appeal to smokers interested in quitting. This consumer subset may be motivated to use VLN™ cigarettes to reduce nicotine exposure, and as a result, potentially aid in facilitating cessation. It is unlikely that current tobacco users who are

not interested in quitting will switch to VLN™ cigarettes or to a smoking cessation product. However, this effect may differ among smokers motivated to quit smoking and who concurrently use NRT and behavioral intervention with VLN™ King cigarettes. Given that menthol in cigarettes contributes to reduced cessation success among NNC cigarette smokers (e.g., Delnevo, Gundersen, Hrywna, Echeverria, & Steinberg, 2011; Faseru et al., 2013; Levy et al., 2011; Trinidad, Perez-Stable, Messer, White, & Pierce, 2010), any potential effect on cessation may be less likely among smokers of VLN™ Menthol King cigarettes, including those who are motivated to quit and who concurrently use smoking cessation aids (Faseru et al., 2013; Okuyemi et al., 2003)

2.4.4. Summary of Overall Behavioral and Clinical Pharmacology Findings

The BCP review concludes that the PMTAs contain adequate information to draw the following conclusions:

- The PK profile of the VLN™ cigarettes indicates a lower abuse liability than the applicant's UB-NNC cigarette comparator.
- Based on the applicant's submitted clinical studies, VLN™ King cigarettes are associated with significantly lower positive subjective effects ratings in adult smokers compared to UB-NNC cigarettes, reducing their abuse liability for youth and non-smokers. The applicant's submitted studies also show that, among adult smokers, VLN™ Menthol King cigarettes have lower positive subjective effects than UB-NNC cigarettes. As menthol in NNC cigarettes facilitates experimentation and progression to regular smoking, it is unknown to what degree menthol may influence likelihood of progressing to regular smoking compared to smoking NNC menthol cigarettes among new and inexperienced users, in particular youth and young adults.
- Menthol and non-menthol NNC smokers who choose to switch to smoking VLNC cigarettes could experience the benefit of significantly reducing their overall exposure to nicotine, potentially reduce their overall smoking, and subsequently, their exposure to non-nicotine HPHCs.
- Lower abuse liability reduces the likelihood that current adult smokers would transition to VLN™ cigarettes or switch completely. Given that current adult smokers are the intended population for VLN™ cigarettes, reduced likelihood of use among adult smokers is likely to reduce youth access to these products and their availability for youth experimentation. As discussed in the BCP review, it has been shown that indirect sources, including stealing or borrowing from an adult, are some of the most common means of youth access to cigarettes. Therefore, reduced adult use would likely reduce youth access through these means.
- Findings from the literature indicate that individuals who smoke VLNC cigarettes demonstrate either no significant differences in smoking topography relative to those who smoke UB-NNC or NNC cigarettes or reductions in tobacco smoke exposure (e.g., lower total puff volume).
- Findings from the literature suggest that smoking VLNC cigarettes may lead to an overall reduction in CPD compared to smoking UB-NNC cigarettes.

- Low subjective appeal, along with increased craving and withdrawal, may prevent current smokers from fully transitioning to VLN™ cigarettes. Data from the literature suggest that those who do switch to VLNC cigarettes reduce their nicotine exposure, may smoke fewer CPD, and lower their nicotine dependence levels compared to those who continue to smoke UB-NNC cigarettes. It is anticipated that smokers who switch to VLNC cigarettes and reduce their overall CPD would also reduce exposure to other non-nicotine HPHCs (see Section 2.4.5).
- Switching to VLNC cigarettes may facilitate abstinence in smokers by increasing motivation to quit and quit attempts. Concurrent use of NRT and behavioral intervention may improve these outcomes. However, among menthol smokers who switch to VLNC cigarettes, the potential effect on cessation may be less likely than with non-menthol VLNC cigarette smokers. Based on literature extrapolated from NNC menthol cigarettes, the reduced likelihood of cessation may occur even in smokers motivated to quit and who concurrently use pharmacotherapy for cessation.

As TPL, I agree with the BCP review conclusions that there is reduced abuse liability, no difference or a slight improvement in smoking topography, and reductions in CPD when using VLNC cigarettes, including the VLN™ cigarettes. I also agree with their conclusions that these factors may lead to an increase in abstinence in some smokers by increasing motivation to quit and quit attempts, but that the low appeal combined with increased craving and withdrawal may prevent other smokers from fully transitioning.

2.4.5. Biomarkers of Exposure (BOE)

BCP also 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 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 six compared to baseline were not significant in the VLN™ King).

A review of the relevant BOE literature cited by the applicant is below.

2.4.5.1. Effect of Switching to VLNC Cigarettes on BOE

Nicotine BOE

Studies ranging from single exposure to 20 weeks of VLNC cigarette use consistently support significantly reduced levels of nicotine BOE, including significantly reduced total cotinine levels and TNE, in participants who switched to smoking VLNC cigarettes compared to NNC cigarettes. A study of smokers (n=31) confined to a hotel for five days confirmed that when participants exclusively switch to smoking VLNC cigarettes, there is a 94% reduction in TNE compared to baseline measurements of participants' use of UB-NNC (Denlinger et al., 2016). The literature

supports that the level of nicotine BOE remains significantly lower for VLNC cigarette smoking compared to smoking UB-NNC/NNC cigarettes even when there is no significant difference in CPD (Donny & Jones, 2009; Hammond & O'Connor, 2014; Hatsukami et al., 2018).

A presentation from the 2019 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.

Non-Nicotine HPHC BOE

Data on BOE for other HPHCs are also available in the literature (e.g., TSNAs [NNN, NNK, NNAL], 3-HPMA [an acrolein metabolite], 1-HOP, mercapturic acid metabolites, PheT [indicator of polycyclic aromatic hydrocarbons]). These studies evaluate outcomes from six weeks through 20 weeks of VLNC cigarette use. Studies of immediate switching to VLNC cigarettes, which, should VLN™ King and VLN™ Menthol King cigarettes be marketed, are more comparable to the marketplace situation, find significant reductions in all measured non-nicotine HPHCs. These reductions in non-nicotine HPHCs are contingent upon a reduction in CPD. Preliminary data from the SRNT presentation discussed above (Denlinger-Apte et al., 2019) also support that VLNC menthol cigarette smokers have significant reductions in non-nicotine HPHCs compared to baseline consistent with a reduction in CPD, although this effect may be to a lesser extent than in VLNC non-menthol cigarette smokers.

2.4.5.2. Dual Use and Non-compliance

Studies from the literature review note that non-compliance with exclusive VLNC cigarette smoking is observed in most participants. 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 experience the effects of reduced dependence on nicotine. For example, despite a high rate of non-compliance in one study (76-78% of participants, based on biochemical verification) TNEs decreased, on average, by 60% from baseline to Week 6 in participants switched to VLNC cigarettes (Nardone et al., 2016). NNAL levels for participants in this study were reduced, but not significantly. 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. Studies do not suggest that smokers would increase their overall CPD or tobacco product consumption if they dual use VLNC and UB-NNC cigarettes. Therefore, dual use would not expose smokers to nicotine levels greater than smoking only UB-NNC cigarettes and 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. 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 dual 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. Dual use of other nicotine-containing products, such as NRT or ENDS, with VLNC cigarettes may aid in reducing overall CPD. 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). Lower levels of total NNAL and NNN have also been observed over eight weeks in participants who used VLNC with non-combusted products compared to NNC cigarettes.

Overall, findings from the literature support that dual use and non-compliance with smoking VLNC cigarettes is high [e.g., 1.46 non-study CPD, 95% confidence interval (0.87, 2.05) in Hatsukami et al. (2018); 1-2 UB-NNC CPD in Denlinger et al. (2016); 5.1 (SD 4.6) non-study CPD in Hatsukami et al. (2017)]; however, nicotine exposure remains significantly reduced in participants who smoke VLNC cigarettes compared to NNC cigarettes.

2.4.5.3. Summary of BOE Findings

While decreases in BOE were found, the extent to which these decreases affect clinical outcomes cannot be determined from the clinical studies. Therefore, no conclusions can be drawn about the long-term health effects associated with VLN™ cigarette use. In BCP's assessment the methodologies used by the applicant to generate data and conduct the literature search to support its application were appropriate.

The literature supports that the reduction in nicotine BOE remains significantly lower for VLNC cigarette smoking compared to smoking UB-NNC/NNC cigarettes even when there is no significant difference in CPD. There are some data suggesting that menthol smokers who switch to VLN™ Menthol King cigarettes would also reduce their nicotine exposure. Additionally, there is some data showing that VLNC menthol cigarette smokers have significant reductions in non-nicotine HPHCs compared to baseline consistent with a reduction in CPD, although this effect may be to a lesser extent than in VLNC non-menthol cigarette smokers. Overall, findings from the literature support that dual use and non-compliance with smoking VLNC cigarettes is high; however, nicotine exposure remains significantly reduced in participants who smoke VLNC cigarettes compared to NNC cigarettes.

2.4.6. Biomarkers of Potential Harm (BOPH)

In a recent publication by Hatsukami et al. (2019) the authors performed a secondary analysis of biomarkers of inflammation, oxidative stress, and hematological parameters collected in the previous described clinical trial (Hatsukami et al. (2018)) in which 1,250 daily smokers were randomized to 1. immediate nicotine reduction, 2. gradual nicotine reduction, or 3. normal nicotine content (control). Hatsukami et al. (2019) analyzed urinary prostaglandin E2 metabolite (PGEM), urinary (Z)-7-[1R,2R, 3R,5S]-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoicacid (8-iso-PGF2α), serum high-sensitivity C-reactive protein (hs-CRP), and hematologic parameters. There were no significant differences in the levels of PGEM, 8-iso-PGF2α, or hs-CRP between the study arms. Statistically significant differences were identified in some hematologic parameters. Only red blood cell distribution width (RDW) showed a consistently lower level in the immediate group versus the gradual and control groups in both AUC and week 20 sensitivity analyses. The magnitude of the change in RDW was small (-0.11 to -0.21%). The authors of the study concluded that "[i]t remains unclear whether switching to very low nicotine cigarettes leads to a short-term reduction in biomarkers of tobacco-related harm."

FDA review noted that robust changes in biomarkers of inflammation, oxidative stress, or hematological parameters in smokers switched to VLN were not identified in this study. Many factors may have contributed to the absence of significant changes, including that 1. the study may have been insufficient duration, 2. the high rates of non-compliance in the VLN study arms may have obscured the results, and 3. the changes in exposure may not have been great enough to impact the chosen markers. The only consistent change detected was a reduction in RDW in the immediate nicotine reduction group versus gradual nicotine reduction and control groups.

RDW is a measure of the degree of variation (anisocytosis) in red blood cell size with a normal range of approximately 11.0 to 15.6%. An increase in RDW indicates greater variation in red blood cell size. RDW may be elevated in a range of conditions, including anemias due to iron, vitamin B_{12}, or folate deficiency. Studies have found an association between RDW and mortality; however, the association is strongest when values on the upper end of the range (≥ 15%) are compared to those on the lower (<12.5%) (Pilling, Atkins, Kuchel, Ferrucci, & Melzer, 2018). In Hatsukami et al. (2019) the AUC mean RDW value in each study group was between 13.86 and 14.00%. The changes in RDW between groups ranged from -0.11 to -0.15% in the AUC analysis and -0.15 to -0.21% in sensitivity analysis. The clinical significance of changes of this magnitude within the normal range for RDW is uncertain.

In the limited evaluation by Hatsukami et al. (2019) there is no indication that VLN use has a detrimental effect on inflammation, oxidative stress, or hematologic parameters compared to NNC cigarettes over 20 weeks. However, no conclusions regarding the short- or long-term health risks of VLN can be made based on the results of this study.

2.4.7. Adverse Health Effects

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 proposed products differ from NNC cigarettes only in the nicotine content. The applicant primarily relies upon two publications, Donny et al. (2015) and Hatsukami et al. (2018), to substantiate risk profile (2015) and Hatsukami et al., (2018), to substantiate safety of VLN™ cigarettes.

It is expected that VLN™ cigarette users 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.[6]

There was one serious adverse experience (SAE) reported during the 6-week switching study. The subject was a 50-year-old white female smoker with 28-year history of cigarette use who had a subarachnoid hemorrhage one day after study completion. Study investigator, Philip Mathew, determined the SAE to be unrelated to the study product because the subarachnoid hemorrhage was due to a ruptured aneurysm. The SAE was determined to be resolved by the date of hospital discharge. In summary, the subject had several underlying risk factors for aneurysmal subarachnoid hemorrhage. Her long history of cigarette smoking, and family history

[6] 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 (U.S. Department of Health and Human Services, 2001).

of aneurysm are more likely to have caused the aneurysm and subsequent SAE than her recent short term VLN™ use.

2.4.7.1. 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 it would be similar to NNC cigarettes. We agree 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.

2.4.7.2. Consumer Use and Potential Misuse

The applicant did not submit any information on human factor studies with VLN™ cigarettes. Per the applicant, these products "perform just like conventional cigarettes . . . [and] will be used in the same manner as conventional nicotine content cigarettes." The human factor issues related to NNC cigarettes leading to misuse or injury are well documented: improper storage, allowing access to unused products by children; 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 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, Martin, & Milano, 2000).

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.

2.4.7.3. Health Risks Associated with Polyuse

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 PMTA submission. No information is provided on BOPHs, adverse events, or published literature that addresses the health risks of use of VLN™ cigarettes when used with other tobacco products. Nonetheless, given that 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.

2.4.7.4. Health Risks Associated with Switching to this Product Compared to Continued Smoking

The health risks are likely the same compared to continued smoking another brand of cigarette. Smokers who completely switch to VLN™ cigarettes may experience weight gain. If smokers do not otherwise decrease their smoking or switch to other nicotine-containing products, then VLN™ cigarette users may have weight gain in addition to the adverse health effects of continued smoking. The BCP review notes in its review (see section on Abuse Liability) that the likelihood that current tobacco product users would completely switch to VLN™ cigarettes is low. The BCP review also notes that this effect may differ in smokers who are motivated to reduce their nicotine exposure or quit smoking. In this scenario of smokers motivated to reduce or eliminate nicotine exposure, the health risks for those who switch to VLN™ cigarettes health risks are likely less harmful than continued smoking. Smoking increases the risk of cardiovascular disease 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, which may contribute to the potential risk of greater thrombosis compared to other cigarettes, an increased risk of thrombosis has not borne out based on adverse event reporting in clinical studies.

For smokers who switch to VLN™ cigarettes, either completely or incompletely, and decrease their CPD, adverse health outcomes may not improve. The relationship between the amount of cigarette smoking and disease is not strictly linear. Health risks are found even with consistent low-level smoking (10 or fewer cigarettes a day) (Rigotti, 2018). For example, small amounts of cigarette smoke exposure can still increase risk for coronary artery disease (U.S. Department of Health and Human Services, 2014) and at least two studies have shown no change in all-cause mortality when smokers halve their daily cigarette consumption (Godtfredsen, Holst, Prescott, Vestbo, & Osler, 2002; Tverdal & Bjartveit, 2006).

2.4.7.5. Health Risks Associated with Switching to this Product Compared to Tobacco Cessation

The applicant did not provide information comparing the short- and long-term health effects of complete or incomplete VLN™ cigarette switching to abstinence. 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 (quitting) by going “cold turkey” or using other means such as behavioral methods or pharmacotherapy can have health risks (e.g., nicotine withdrawal syndrome, weight gain, depression, cough, mouth ulcers (Rigotti, 2018)) but the benefits of abstinence (quitting) far outweigh these risks.

Lastly, VLN™ cigarettes could deter smokers from abstinence if these products are perceived as a safer choice than NNC cigarette smoking due to decreased nicotine exposure. This may be especially true in people who despite multiple quit attempts have not been able to quit

smoking. The applicant did not address the issue of VLN™ cigarette use deterring abstinence attempts.

2.4.7.6. Health Risks Associated with Switching to Product Compared to Cessation Medication

The applicant did not provide clinical data to evaluate the relative health risks of switching to VLN™ cigarettes compared to using cessation medication. 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 medications is far preferable than smoking any combustible products, including VLN™ cigarettes. FDA-approved smoking cessation medications 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, it is possible that VLN™ cigarettes could deter smokers from abstinence with or without FDA-approved smoking cessation medications. 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 cigarette 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, which may aid in future quite 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.

2.4.7.7. Summary of Adverse Health Effects

Overall, if smokers who switch to the VLN™ cigarettes decrease their use and/or ultimately quit, there would likely be improved health benefits. If, on the other hand, cigarette smokers who completely switch to VLN™ cigarettes use them in the same way as NNC cigarettes, it is possible that they may have weight gain, but with the added adverse health consequences of continued smoking. According to the BCP review (see section on Abuse Liability), the likelihood of this latter scenario is likely low.

2.4.8. Likelihood of Product Misuse or Malfunction

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. As discussed in the medical review, the human factors issues related to cigarettes leading to misuse or injury are well known: improper storage, allowing access to unused products by children; 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 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 VLNs™ cigarettes because they have no unique use characteristics that differ from NNC cigarettes.

2.4.9. Bioresearch Monitoring (BIMO) Inspection

OS reviewers did not identify any substantive concerns pertaining to the submitted clinical studies and did not recommend BIMO inspection. FDA's Office of Compliance (OCE) review of the submission did not reveal any data integrity or human subject protection concerns and agreed with OS reviewers that BIMO inspections for the protocols submitted and associated sites are not warranted.

2.4.10. Summary of Individual Health Findings

The BCP review concludes:

- Smokers who switch to smoking VLNC cigarettes have reduced exposure to nicotine compared to smoking UB-NNC cigarettes.
- As a result of reducing nicotine exposure, switching to smoking VLNC cigarettes can lead to smoking fewer overall CPD compared to UB-NNC cigarettes. Smokers who reduce their overall CPD by smoking VLNC cigarettes may subsequently reduce non-nicotine HPHCs (e.g., NNAL, NNK, 3-HPMA).
- Nicotine exposure is also reduced in smokers who do not reduce their overall CPD when switching to VLNC cigarettes and in smokers who dual use UB-NNC cigarettes or other tobacco products; however, non-nicotine HPHCs are not reduced in smokers who do not reduce their overall CPD when switching to VLNC cigarettes.
- The reduced nicotine exposure in smokers of VLNC cigarettes may be associated with reduced dependence levels and facilitate abstinence in smokers motivated to quit. Concurrent use of NRT and behavioral intervention may improve cessation outcomes in VLNC cigarette smokers motivated to quit. However, given the role of menthol in reduced cessation success among NNC menthol smokers, it is anticipated that any potential effect on abstinence would be less likely among VLN™ Menthol King cigarette smokers, even those who are motivated to quit and concurrently use NRT.
- Despite high rates of non-compliance, studies still report an average 60% reduction in nicotine exposure over six weeks of use and a reduction in measured non-nicotine HPHCs; the effect on non-nicotine HPHCs remains contingent upon an overall reduction in CPD.
- Some studies find that consumers who dual use VLNC and UB-NNC cigarettes may not decrease their overall cigarette consumption (i.e., smokers tend to replace some of the UB-NNC cigarettes with VLNC cigarettes). Nicotine exposure is reduced in consumers who primarily smoke VLNC cigarettes, but do not decrease their overall CPD compared to their UB-NNC cigarette consumption. However, levels of non-nicotine HPHCs are not reduced compared to UB-NNC cigarettes in VLNC cigarette smokers who do not reduce their overall cigarette consumption.

As TPL, I agree with the BCP review conclusions that there is a reduction in nicotine BOE when smokers switch to VLNC cigarettes. When the switch to VLNC cigarettes results in a decrease in CPD, there is also a decrease in other, non-nicotine HPHC BOE. These reductions are seen despite high rates of non-compliance in studies. Together these results indicate that using either of the VLN™ cigarette products would be expected to reduce the nicotine exposure in

individuals, potentially leading to reductions in dependence and CPD. The reduction in CPD could lead to a decrease in other non-nicotine HPHC BOE.

The medical review concludes:

- Regarding individual health risk from use of VLN™ cigarettes, there are limited data available in the published literature. VLN™ cigarette users will likely have similar short- and long-term health effects as those that occur with NNC cigarette smoking if used in the same manner given that the unique aspect of these products is the low nicotine content.
- Smokers who switch exclusively to VLN™ cigarettes may experience the adverse consequences of weight gain in addition to the adverse health effects of continued smoking.
- Smoking increases the risk of cardiovascular disease and thrombosis. While in vivo and in vitro studies have indicated that VLN™ cigarettes may cause increased platelet activation than cigarettes with higher nicotine content, which may contribute to greater risk of thrombosis compared to other cigarettes, adverse event data are insufficient to draw meaningful clinical conclusions regarding whether there is increased risk of thrombosis.
- Smokers who completely switch to VLN™ cigarettes may experience nicotine withdrawal. Adverse event data from applicant-sponsored studies and from the published literature are limited but suggest that some adverse events may relate to nicotine withdrawal. See Section 6 for more information about adverse events in the published literature. There is little experience with VLN™ cigarettes to determine whether they may have adverse public health consequences beyond relapse to NNC cigarettes or other nicotine sources, such as ENDS, or the use of other substances to mitigate withdrawal symptoms.
- Non-users who are involuntarily exposed will likely experience the same adverse health effects as exposure to tobacco smoke from NNC cigarettes.

The medical review concludes that VLN™ cigarettes are combusted tobacco products composed of tobacco leaves containing less nicotine. These products will likely have the similar adverse health effects as smoking NNC cigarettes if used in the same manner. It is possible that these products may decrease nicotine dependence among users. Smokers who completely switch to VLN™ cigarettes may experience nicotine withdrawal. Cigarette smokers who completely switch to VLN™ cigarettes and use them as their sole source of nicotine may, over time, have weight gain similar to smokers who quit, but with the added adverse health consequences of continued smoking. This is a theoretical risk, unsupported by current evidence.

As TPL, I agree with the medical review. Low nicotine cigarettes are not new to the market. Several low nicotine cigarettes have been available in the past with limited public interest. There are limited data available related to short-term health effects of VLN™ cigarettes. As an example, per the medical review, smokers who switch exclusively to VLN™ cigarettes may experience the adverse consequences of weight gain in addition to the adverse health effects of continued smoking. That said, the likelihood that current tobacco users would switch

completely to these products is low, however, for those that are able to switch to VLN™ cigarette use, the reduction in nicotine exposure and dependence is thought to outweigh the potential weight gain associated with low nicotine tobacco product use. Furthermore, VLN™ cigarettes have been used in various clinical studies for several years; no health-related short-term issues uniquely related to VLN™ cigarettes were identified. There are limitations to the clinical studies conducted by the applicant; however, there are practical limitations to the number, size, and nature/design of clinical studies that can realistically be completed during new product development. Although limited, the data available in the applicant's clinical studies do not raise concerns or identify specific health-related issues uniquely related to VLN™ cigarettes compared to combusted cigarettes.

2.5. Population Health

2.5.1. Likelihood of Use by Current Cigarette Smokers

The epidemiology review (section 3.2) states that the applicant did not submit any observational studies on the likelihood of use of VLN™ cigarettes for current tobacco users. However, a randomized-controlled trial, by Hatsukami et al. (2018), showed that in a forced-switching environment, daily smokers who switched to VLNC cigarettes reduced their cigarette consumption by around 50% after 20 weeks of use. The immediate reduction group had greater withdrawal symptoms, greater use of non-study cigarettes and higher dropout rates compared to the gradual nicotine reduction group (32% vs 19%). Despite the success of nicotine reduction of these forced-switching studies, in a real-world setting where NNC cigarettes are available, it is unlikely that current smokers of NNC cigarettes will switch to this product due to the low appeal of VLN™ cigarettes.

The applicant did not provide epidemiological evidence regarding the likelihood that tobacco users who adopt VLN™ cigarettes will switch to or switch back to other tobacco products, such as NNC cigarettes, that may present higher levels of individual risks if consumers increase the number of CPDs when switching to NNC cigarettes. In addition, the applicant did not provide observational data on the transition of VLN™ cigarette use back to NNC cigarette use. However, in a real-world setting where NNC cigarettes are available, there is a high likelihood that current smokers of NNC cigarettes who may adopt VLN™ cigarettes will switch to or switch back to other tobacco products such as NNC cigarettes due to the low appeal of VLN™ cigarettes. Epidemiologic data regarding the likelihood that users of any tobacco product who may have otherwise quit or switch to a smoking cessation product would instead use the VLN™ products is not available at this time. Available short-term data indicate that polytobacco use of VLNC and other tobacco products is likely and that, for some tobacco product users, availability of VLNC, despite polytobacco use, can lead to reduction in cigarette consumption, increased quit attempts, and in some cases spontaneous cessation of tobacco products. Long term epidemiologic data on use behavior of a proposed product is typically not available premarket, thus, postmarket reporting may assist in monitoring use transitions.

The BCP review Section 4.1 discusses the results from applicant-submitted clinical studies, as well as the larger VLNC literature, to address the likelihood of use by current cigarette smokers.

After reviewing both the studies and the literature, BCP determined that VLN™ cigarettes were associated with lower abuse liability compared to UB-NNC cigarettes as evidenced by lower plasma nicotine uptake (C_{max}, AUC), positive subjective effects ratings (e.g., pleasant, satisfying, calm), and likelihood of future use. VLN™ cigarettes were associated with a similar abuse liability profile as 4 mg nicotine gum, as evidenced by similar positive subjective effects ratings. As discussed in Section 3.2, the larger VLNC literature corroborates the applicant's data on VLN™ cigarettes. In extended duration studies, when participants are provided with a sufficient supply of VLNC cigarettes at no cost, there are high levels of non-compliance wherein participants choose to pay for NNC cigarettes rather than use the VLNC cigarettes provided free of charge. Taken together, the data suggest that current smokers not interested in quitting or reducing their nicotine exposure have a low likelihood of initiating use of VLN™ cigarettes. However, current smokers interested in reducing their nicotine exposure and motivated to quit smoking may be the group most likely to start using VLN™ cigarettes.

The applicant's clinical abuse liability studies find that VLN™ cigarettes are associated with low subjective effects ratings and increases in cigarette craving and are not reliably chosen over UB-NNC cigarettes. Specifically, VLN™ cigarettes have lower positive subjective effects ratings (e.g., pleasant, satisfying, calm) compared to UB-NNC cigarettes and a low likelihood of future use. These findings are supported by studies of VLNC cigarettes in the literature. Long-term studies on VLNC cigarettes (i.e., six to 20 weeks) indicate a high rate of non-compliance in smoking VLNC cigarettes, with product satisfaction being a predictor of non-compliance. Due to the low consumer satisfaction and low abuse liability of VLN™ cigarettes, the likelihood that current tobacco users would switch completely to these products is low. It is anticipated that some current tobacco users who adopt these products would switch back to smoking their UB-NNC cigarettes. However, this effect may differ in smokers who are motivated to reduce their nicotine exposure or quit smoking. For those individuals that are able to switch to using VLN™ cigarettes, studies show that there can be a reduction in nicotine exposure and dependence with a reduction in overall CPD use.

2.5.2. Summary of Likelihood of Use by Current Cigarette Smokers

As TPL I agree with the epidemiology and BCP reviews' conclusion that it is unlikely that many current cigarette smokers would completely switch to VLN™ cigarettes. This is supported by the low appeal, consumer satisfaction, and abuse liability of VLN™ cigarettes found both in the two clinical studies provided as well as in the broader literature on VLNC cigarettes. Current smokers interested in reducing their nicotine exposure and motivated to quit smoking may be the group most likely to start using VLN™ cigarettes.

2.5.3. Poly-use of VLN™ cigarettes and cigarettes or other tobacco products

Both the epidemiology review (section 3.2) and the BCP review (section 4.1) note that there are very few clinical studies assessing the effects of VLNC cigarettes on other tobacco product use. One study was designed to assess other tobacco product use among smokers not interested in quitting; participants were assigned to smoke LNC cigarettes (1.3 mg nicotine per gram of tobacco) or NNC cigarettes and were provided with access to combusted or non-combusted tobacco products. Participants who received LNC cigarettes used more alternative combusted

and non-combusted tobacco products. However, these participants also smoked fewer total combusted tobacco products and had more quit-attempts. Furthermore, tobacco toxicant levels in participants who received LNC cigarettes and only non-combusted products were significantly lower than those in participants who received NNC cigarettes; toxicant levels in participants who received LNC cigarettes and had access to both combusted and non-combusted products did not differ from those in the NNC cigarette group. In addition, a study of nondaily smokers found that those randomized to receive LNC cigarettes for 10 weeks (1.3 mg nicotine per gram of tobacco) were more likely to use ENDS compared to those randomized to an NNC group (Shiffman et al., 2018). Finally, clinical studies report high rates of non-compliance with VLNC cigarettes, even when provided free of charge, suggesting that dual use with UB-NNC cigarettes may be common.

2.5.3.1. Summary of Poly-use

As TPL I agree with the epidemiology and BCP reviews that there is evidence that smokers who use VLN™ cigarettes may use other tobacco products including NNC cigarettes; however, their total combusted tobacco product consumption and toxicant exposure are not likely to increase and may be lower if the polyusers reduce overall CPDs compared to those in smokers who continue to smoke UB-NNC cigarettes

2.5.4. Use by Former or Never Smokers

The epidemiology review notes that the applicant did not provide data from national surveys and epidemiological studies to suggest that never tobacco users (particularly youth or young adults) will not take up VLN™ cigarettes. The applicant also did not provide any evidence to address the likelihood that never users who take up VLN™ cigarettes will switch to other tobacco products that present higher levels of individual health risk. Even though VLN™ cigarettes are lower-nicotine products, VLN™ cigarettes are still combustible tobacco products, and never tobacco users would be exposed to all of the same non-nicotine HPHCs that are in the NNC combusted cigarettes.

On the other hand, the BCP review, in order to discuss the potential impact on former or never-smokers, extrapolated from the literature on use and appeal in current smokers, as all studies in the literature assessing the use and appeal of VLNC cigarettes involved current cigarette smokers. The BCP review states that a large minority of subjects (over a third) of non-daily smokers provided with VLNC cigarettes at no cost were non-compliant with exclusive VLNC cigarette use. In extended duration studies, when participants are provided with a sufficient supply of VLNC cigarettes at no cost, there were high levels of non-compliance wherein participants choose to pay for NNC cigarettes rather than use the VLNC cigarettes provided free of charge. Additionally, in the applicant-submitted clinical studies with current smokers, VLN™ cigarettes were associated with lower abuse liability compared to UB-NNC cigarettes as evidenced by lower plasma nicotine uptake (C_{max}, AUC), positive subjective effects ratings (e.g., “pleasant,” “satisfying,” “calm”), and likelihood of future use. Extrapolating from this limited literature and submitted clinical studies in current smokers, these data suggest a low likelihood that VLN™ King cigarettes would promote initiation and progression to regular use among consumers who have never used tobacco products.

2.5.4.1. Summary of Use by Former or Never Smokers

As TPL I agree with the epidemiology review that there are no data that directly look at the likelihood that former or never users would take up VLN™ cigarettes, or the likelihood that those in this population who do use these products would switch to products with high levels of individual health risk (such as NNC combusted products). However, I agree with the BCP review that the information provided on current users may be informative to the former and never user population and that data suggest a low likelihood that VLN™ cigarettes would promote initiation and progression to regular use among consumers who have never used tobacco products.

2.5.5. Use by Vulnerable Populations (Youth and Mental Health Populations)

2.5.5.1. Youth

The epidemiology review states that the applicant did not provide data on the impact of the name "VLN™" or "Moonlight®" on never tobacco users including youth. It is possible that youth may believe that these cigarettes might be "safer" than NNC cigarettes, and youth who experimented with VLN™ cigarettes could transition to NNC cigarette smoking. Furthermore, the applicant did not provide information on how menthol VLN™ smoking could impact the likelihood of VLN™ use by youth. The applicant suggested that VLN™ cigarettes are less reinforcing and less appealing to youth; however, Epidemiology notes that menthol cigarette smoking among youth could facilitate progression or transition to more established smoking (U.S. Department of Health and Human Services, 2012). The 2012 Surgeon General Report "Preventing Tobacco Use Among Youth and Young Adults" shows that menthol use is disproportionally higher in youth and young adults compared to older adults. Initiating menthol smoking could put youth and young adults at risk for becoming established smoking later in life (U.S. Department of Health and Human Services, 2012).

Section 4.1 of 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. However, studies support that menthol in NNC cigarettes facilitates increased experimentation and progression to regular smoking among youth and young adults and contributes to greater dependence in youth smokers (e.g., Hersey et al., 2006; Wackowski & Delnevo, 2007).

Additionally, the applicant submitted a summary of a recent published study as part of

amendment PM0000514, reviewed by TPL only as a late amendment, discussing youth perception of VLNC cigarettes. 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, the current 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 were associated with reduced abuse liability compared to usual brand cigarettes in this group of adolescent smokers.

Given that current adult smokers are the intended population for VLN™ cigarettes, reduced likelihood of use among adult smokers is also likely to reduce youth access to these products and their availability for youth experimentation. Indirect sources, including stealing or borrowing from an adult, are some of the most common means of youth access to cigarettes (Castrucci, Gerlach, Kaufman, & Orleans, 2002; Cummings, Sciandra, Pechacek, Orlandi, & Lynn, 1992; Lenk, Toomey, Shi, Erickson, & Forster, 2014). Therefore, reduced adult use would likely reduce youth access through these means.

2.5.5.2. Mental Health Populations

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 (i.e., individuals with depression, schizophrenia, 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. 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.

2.5.5.3. Summary of Use by Vulnerable Populations

As TPL I note the concerns raised by the epidemiology review that information on perception of the name "VLN" was not provided. After the epidemiology review was initially completed, the applicant amended the PMTA to change the proposed brand name from "VLN" to "Moonlight." There was no information on the perception of the new name provided. If individuals become aware that these products are low nicotine cigarettes, there may be individuals who consider that low nicotine products are "safer" tobacco products and experiment with these products first. While nicotine dependence has been shown to develop rapidly among adolescents following exposure to NNC cigarettes, I agree with the BCP review that 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 progress to established smoking due to their lower abuse liability profile. There is evidence that in NNC cigarettes menthol can facilitate progression to use and transition to established smoking due to the synergistic effect of menthol on the reinforcement of nicotine. However, as the VLN™ Menthol King cigarettes have ~95% less nicotine than NNC cigarettes currently on the market and at a dose that is considered minimally addictive, there would not likely be the same reinforcement of the menthol compared to NNC cigarettes. Stated alternatively, although the menthol in VLN™ Menthol King cigarettes will still have the effect of making it easier to tolerate the inhalation of the combusted product, youth will likely find both VLN™ products less appealing due to lower nicotine levels and be less likely to become established cigarette smokers.

As TPL I agree with the epidemiology and BCP reviews that note for similar VLNC cigarettes 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.

2.5.6. Population Modeling

The epidemiology review notes that the applicant did not conduct any population modeling of tobacco product use behavior. The applicant states that VLN™ cigarettes are not attractive to former smokers and never smokers, and that "the sales of the product without claims will be negligible and there will be no impact on the population as a whole." The epidemiology review notes that in the real-world setting (in absence of any nicotine standard), where NNC cigarettes are available it is uncertain whether most current cigarette smokers will switch to VLN™ cigarettes.

2.5.7. Summary of Population Health Findings

The epidemiology review states that the PMTAs do not contain sufficient information about the VLN™ cigarettes as the applicant did not conduct or include observational studies or population modeling of tobacco product use behavior and concluded that marketing the product without claims would have no impact on the population as a whole. The epidemiology reviewer states that in the absence of a nicotine standard, where NNC cigarettes are available, it is uncertain whether most current cigarette smokers will switch to VLN™ cigarettes. Therefore, the likelihood of the use of VLN™ cigarettes among never tobacco users, including youth and young adults is unknown. Additionally, the applicant did not provide information on how VLN™ Menthol King cigarette smoking could impact the likelihood of VLN™ cigarette smoking by youth. The 2012 Surgeon General's Report has summarized that use of NNC menthol cigarette smoking among youth may facilitate progression or transition to established cigarette smoking (U.S. Department of Health and Human Services, 2012). Given that VLN™ cigarettes are combustible cigarettes, never tobacco users including youth who start experimenting or using VLN™ cigarettes would be exposed to the same non-nicotine HPHCs that are in NNC cigarettes.

As TPL I disagree that there is insufficient data related to VLN™ cigarettes and similar VLNC cigarettes to reasonably anticipate likely population health. VLNC cigarettes were on the U.S. market previously, in an environment where both NNC and VLNC cigarettes existed simultaneously. Furthermore, there are clinical studies evaluating VLN™ cigarettes and similar VLNC cigarettes manufactured by the applicant, although in controlled environments, related to tobacco use patterns and trends as well as consumer studies conducted by the applicant and other investigators. Thus, there is information about likely use by various populations to draw upon in this review. Overall, it is anticipated that uptake of VLN™ cigarettes without any claims would be low. Nevertheless, based on clinical studies, it appears that there is a portion of smokers that may be able to use VLN™ cigarettes as a transitional product to cut down CPD and eventually quit. Given the very low nicotine available from these cigarettes, which are non-reinforcing, and general low likeability of taste, it is not expected that youth or never smokers would experiment and transition to regular use even in the presence of menthol flavor and, at minimum, any transition would be less than in NNC cigarette experimenters. According to the 2018 Monitoring the Future National Survey Results on Drug Use 1975-2018, cigarette smoking among youth was declining from 2002 to 2010 while Quest cigarettes were on the market

(Johnston et al., 2019). In addition, there is a study that examined college students' preferences on light cigarettes or potential reduced exposure products including Quest and Eclipse that they found college students had lower positive expectancy (less likely to use) with Quest cigarettes (O'Connor et al., 2007). Cigarette smoking among youth has steadily continued to decline in the past few decades, including the time period that a VLNC cigarette (Quest) was on the market. The introduction of VLNC cigarettes did not appear to have had a negative impact on declining smoking rates with youth.

2.6. Product Labeling, Consumer Comprehension, and Marketing Plan

2.6.1. Proposed PMTA Labeling

The applicant submitted specimens of proposed labeling for the PMTAs. OCE Division of Promotion, Advertising, and Labeling (DPAL) reviewed these specimens of proposed labeling and did not note issues of concern with the labeling, standing alone. However, DPAL noted concern that "VLN" displayed on the submitted labeling, which appears to stand for "very low nicotine," in conjunction with other representations, may render the product a modified risk tobacco product. The applicant indicates that "VLN™" stands for "Very Low Nicotine", and has stated the following:

1) In the text of the PMTA, under a subheading titled "Product Description," the applicant states "22nd Century developed the VLN™ cigarettes that are the subjects of this application. The VLN™ cigarettes (Menthol King and regular King (non-menthol) cigarettes) are also exactly the same as the NRC102 and NRC103 SPECTRUM® very low nicotine research cigarettes" (Page 32, PMTA)
2) The applicant also states, "Very Low Nicotine Tobacco destined for VLN™ brand cigarettes is also tested for its nicotine content" (Page 93, PMTA).
3) A press release dated December 5, 2018 announcing the filing of the PMTA is titled "22nd Century Files Premarket Tobacco Application (PMTA) with the FDA" The press release explains the application is for cigarettes to be marketed "under the proposed brand name VLN™ (the product name is subject to FDA approval). 22nd Century's proposed VLN™ cigarettes – the subject of the PMTA – are made with 22nd Century's proprietary VLN™ tobacco and, as a result, contain very low levels of nicotine" (https://ir.xxiicentury.com/press-releases/detail/356/22nd-century-files-premarket-tobacco-application-pmta) . The December 5, 2018 press release announcing the filing of an PMTA for "Very Low Nicotine Content Cigarettes" can also be found on the firm's website. (https://ir.xxiicentury.com/press-releases/detail/356/22nd-century-files-premarket-tobacco-application-pmta)

DPAL notes that labeling and/or advertising that represents explicitly or implicitly that a tobacco product contains a reduced level of a substance or presents a reduced exposure to a substance (e.g. nicotine) would render that product a Modified Risk Tobacco Product ("MRTP") (sec. 911(b)(2)(A)(i)(II)). Additionally, tobacco product labeling and/or advertising that uses the descriptors "light," "low," or "mild" or similar descriptors would render that product an MRTP (sec. 911(b)(2)(A)(i)). It is the applicant's responsibility to ensure that the products comply with

the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations, such as the Federal Cigarette Labeling and Advertising Act.

On October 2, 2019, the applicant amended their PMTAs to change the proposed brand name from "VLN™" to "Moonlight" (PM0000549). This amendment also included specimens of proposed labeling which reflected the change in brand name. DPAL reviewed these specimens of proposed labeling and other representations made by the applicant and generally did not note any issues of concern. However, DPAL is concerned that the brand name "Moonlight" may appear on other labeling or advertising in a manner that highlights the descriptor "light," and may potentially be marketed as such without an MRTP order in effect. It is the applicant's responsibility to ensure that the products comply with the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations, such as the Federal Cigarette Labeling and Advertising Act.

As TPL I agree with OCE DPAL's review that there is a potential for the applicant to use modified risk language in product communications related to VLN™ as well as Moonlight given publicly existing product communications language. However, I do not feel this is a limitation that should prevent a marketing authorization in that it is the applicant's responsibility to ensure that the products in the United States comply with the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations, such as the Federal Cigarette Labeling and Advertising Act. We may inform the applicant further on use of potential modified risk language by noting in a marketing order letter, should one be issued, that "light" and "very low nicotine" is considered modified risk language and may not be used to describe the proposed products without appropriate authorization in place. At this time, the labeling does not otherwise appear to be false or misleading.

2.6.2. Consumer Perception

22nd Century submitted one perception study conducted for the modified risk tobacco product application (MRTPA) for VLN™ cigarettes that examined outcomes relevant to the social science review for this PMTA: "Quantitative Study to Develop VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users." The purpose of this consumer perception study was to measure responses to versions of the VLN™ label and messaging within populations of: 1. adult smokers with an intention to quit, 2. adult smokers without any intention to quit, 3. adult former smokers, and 4. adult never smokers. The applicant notes that the total sample was 29,219 participants, with approximately 7,000 participants per concept. However, Table 1 of the application indicates that there were approximately 3,500 participants per control condition and slightly more than 7,000 participants for each experimental condition. Specifically, the study aimed to assess risk perceptions and intent to use for VLN™, Marlboro Gold and four comparator categories (NNC cigarettes, NRT, ENDS, and moist snuff). There were two control conditions. One control group was shown a Marlboro Gold pack and the other group was shown a VLN pack without claims. The data related to the VLN™ pack without claims is most pertinent for these PMTAs.

Secondary objectives were to estimate the impact of VLN™ cigarettes after exposure to the product among adult never smokers, adult never smokers legal age to 25 years old, adult former smokers (recent and long-term), adult smokers motivated to quit, and adult smokers with no intention to quit.

However, in an amendment submitted on September 13, 2019 (PM0000544), the applicant noted (b)(4) .

The applicant also submitted a literature review that addressed consumers' beliefs about the health risk of using cigarettes relative to other tobacco products and the ability of consumers to understand modified risk claims. For the PMTA, only the first objective was examined by the social science review.

The social science review concludes that the applicant submitted a literature review and one perception study that examined outcomes potentially relevant to the evaluation of VLN™ cigarettes from the social science perspective. (b)(4) , there is no information to evaluate the appeal and perception of VLN™ specifically from the social science perspective in the content of this PMTA.

As TPL, I agree with the social science review that there are limitations to the consumer perception study provided for the PMTA and is not relevant provided the name change proposed. Useful conclusions can nonetheless be made related to potential impact of VLN™ cigarettes on the population as VLNC cigarettes are not a new product. Products similar to VLN™ cigarettes have been marketed in the US in early 2000s with limited marketing success, generally due to lack of desirable flavor and likeability. There is limited information available in the literature indicating that for some individuals, especially those motivated to quit, the VLNC cigarettes offer a way to cut down on tobacco products, which may lead to quitting. To date, significant transitions of undesirable behaviors such as youth or never user initiation of VLNC cigarettes and former users re-initiating do not appear to be of concern. In particular, the lower abuse liability profile of VLNC cigarettes make it less likely that experimentation of these cigarettes by youth would encourage regular use compared to NNC cigarettes.

2.6.3. Required Labeling

The cigarettes, if authorized, would bear the rotating Surgeon General's warnings required under the Federal Cigarette Labeling and Advertising Act (FCLAA).

3. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Dr. Kimberly Benson on October 29, 2019. The FONSI was supported by an environmental assessment prepared by FDA on October 29, 2019.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1. Conclusions

In its applications for the VLN™ cigarettes, the applicant provided detailed information about the manufacturing process. This information describes adequate process controls and quality assurance procedures to help ensure that the VLN™ cigarettes are manufactured consistently to meet the applicant's specifications. To verify nicotine data, confirmatory testing was conducted at FDA's STL. Although there were methodological differences between the applicant's testing and the FDA testing, the results were similar. The STL data shows that the VLN™ cigarettes have 97-98% lower nicotine levels in tobacco and mainstream smoke than the top six comparator cigarette brands. The STL nicotine data also supports the applicant's statement that the proposed products contain 95% less nicotine.

The results of a toxicology evaluation demonstrate that the overall noncancer hazards and cancer risks associated with toxicant exposure due to use of VLN™ King and VLN™ Menthol King cigarettes are likely similar to those due to use of the six commercially marketed NNC cigarette comparators in this application. Combining the submitted evidence, the overall toxicological risk to users (i.e., the potential health hazards and risks associated with toxicant exposure), assuming they completely switch to VLN™ King and VLN™ Menthol King cigarettes, are likely similar to those for users of the six commercially marketed NNC cigarette comparators. However, if there was evidence to support that users would switch completely to VLN™ cigarettes, then potential reductions in CPD may result in lower toxicant risks in comparison to the use of the six comparators.

Noncancer hazards and cancer risks to dual users of tobacco products, where at least one product is VLN™ King or VLN™ Menthol King cigarettes, are also likely to be similar or less than smoking the six commercially marketed NNC cigarette comparators, to the extent that the use of such additional tobacco products or NRT is less harmful than use of the six comparators. By extension of the comparative risks for complete switchers, or for dual users in which one product is VLN™ King or VLN™ Menthol King cigarettes, the associated exposures and risks posed to non-users through SHS are also likely similar to or less than what they may experience through exposure to SHS from the six comparators. The extent to which this is true for dual users is, however, also dependent on the likelihood that the additional tobacco products they use are less harmful than the six comparators. In other words, if by using VLN™ King or VLN™ Menthol King cigarettes the consumer dual uses less harmful products (i.e., non-combusted products) than the six comparator products, then the associated exposures and risks posed to non-users through SHS would be less.

Using VLN™ King and VLN™ Menthol King cigarettes compared to quitting tobacco use or switching to NRT would increase harm, as toxicant exposures would be similar to exposure resulting from the use of the six comparators, if product use frequency and amount are the same. However, in the event that a regular cigarette user switched to VLN™ King and VLN™ Menthol King cigarettes, and reduced their CPD, their toxicant exposure would also be expected to be reduced. For non-users seeking to initiate smoking by using VLN™ King and VLN™ Menthol King cigarettes, if they proceeded to using the products similarly to those

initiating with NNC cigarettes, toxicant exposures and associated health risks would likely be similar as those of naive users who initiate smoking with one of the six comparators. However, due to the reduced nicotine levels, non-users experimenting with VLN™ King and VLN™ Menthol King cigarettes would be at less risk for developing dependence to these products and becoming established users than those initiating with NNC cigarettes.

The PK profile and lower positive subjective effects ratings of the VLN™ cigarettes indicate a lower abuse liability than the applicant's UB-NNC cigarette comparator. Menthol and non-menthol NNC smokers who choose to switch to VLN™ cigarettes would experience the benefit of significantly reducing their overall exposure to nicotine, potentially reducing their overall smoking, and subsequently, their exposure to non-nicotine HPHCs. However, the low subjective appeal, along with increased craving and withdrawal, may prevent current smokers from fully transitioning to VLN™ cigarettes.

Youth may believe that VLNC cigarettes might be "safer" than NNC cigarettes, and some youth who experimented with VLN™ cigarettes could transition to NNC cigarette smoking. 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. 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. The applicant did not provide information on how menthol could impact the likelihood of VLN™ use by youth, however, in the adult study of VLN™ Menthol King data showed these cigarettes have lower positive subjective effects than UB-NNC cigarettes though the reduction is less than compared to VLN™ King cigarettes.

Data provided in the literature cited in the application indicate that there is a reduction in nicotine BOE when smokers switch to VLNC cigarettes. When the switch to VLNC cigarettes results in a decrease in CPD, there is also a decrease in other, non-nicotine HPHC BOE. These reductions are seen despite high rates of non-compliance in studies. Together, these results indicate that using either of the VLN™ cigarette products would be expected to reduce the nicotine exposure in individuals, potentially leading to reductions in dependence and CPD. The reduction in CPD could lead to a decrease in other non-nicotine HPHC BOE.

The applicant's consumer perception study had (b)(4) and specific appeal of VLN™ cigarettes could not be assessed. Nonetheless, evidence from the current smoker literature and studies, as well as previous U.S. markets that had VLNC cigarette products, may be used to reasonably anticipate outcomes of the availability of VLN™ cigarettes on current, former, and non-users of cigarettes. Overall, it is anticipated that uptake of VLN™ cigarettes without any claims would be low. Nevertheless, based on clinical studies, it appears that there is a portion of smokers who may be able to use VLN™ cigarettes as a transitional product to cut down CPD and eventually quit. Given the very low nicotine available from these

cigarettes, which are non-reinforcing, and general low likeability of taste, it is not expected that youth, former, or never smokers would experiment and transition to regular use even in the presence of menthol flavor and, at a minimum, any transition would be less than that in NNC cigarette experimenters.

If smokers who switch to the VLN™ cigarettes decrease their use, there would likely be improved health benefits. If smokers who switch to the VLN™ cigarette eventually quit tobacco product use, there would certainly be improved health benefits. If, on the other hand, cigarette smokers who completely switch to VLN™ cigarettes use them in the same way as NNC cigarettes, it is possible that they may have weight gain due to the lower nicotine but with the added adverse health consequences of continued smoking, although the likelihood of this scenario is likely low given the high prevalence of dual use in studies. While the risk of potential increased platelet activation was noted as a possible unintended consequence, limited clinical evidence to date does not indicate an increased risk of thrombosis relative to NNC cigarettes. Continued adverse event reporting may be informative.

4.2. Recommendation for Marketing

As discussed in this review, I recommend the PMTAs be authorized. None of the grounds specified in Section 910(c)(2) of the FD&C Act apply. Specifically, I find the following:

1. Permitting the marketing of the products is appropriate for the protection of the public health, as described in Section 910(c)(4) of the FD&C Act;
2. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in 906(e);[7]
3. Based on a fair evaluation of all material facts, the labeling is not false or misleading in any particular;[8] and
4. The products do not fail to conform to a tobacco product standard in effect under Section 907 of the FD&C Act.

I recommend FDA grant marketing authorization for the products described in the STNs, subject to the changes to the products' package labels and advertisements, as described above:

1. PM0000491
2. PM0000492

4.3. Postmarketing Requirements

The following language should be included in the marketing authorization:

[7] FDA has not yet promulgated any regulations under Section 906(e) of the FD&C Act.

[8] When FDA promulgates a final rule with respect to health warnings for cigarettes, FDA will reevaluate the conditions of marketing with respect to warnings for the products subject to this order.

4.3.1. Recordkeeping and Retention

Under section 910(f) of the FD&C Act, we are requiring in these orders that you establish and maintain the records listed below. At any time during the retention period described in this order, FDA may request that you provide any of the documents described below. In addition, under section 704 of the FD&C Act, FDA may inspect your establishment(s) and request to inspect any record(s) described below.

The following records must be retained cumulatively, that is, for a period of not less than four years from the date of distribution of the *last batch of each product* subject to this order, as described below. These records must be legible, in English, and available for inspection and copying by officers or employees duly designated by the Secretary, upon request.

Type of Record	**Description**	**Retention Period**
Prior PMTAs	Each PMTA submitted prior to marketing order	Four years from the date of distribution of the last batch of each product subject to this order
Postmarket reports	Postmarket periodic reports submitted to FDA, including documents such as: status report of ongoing studies conducted by, or on behalf of, the applicant; adverse experience reports and all relevant documentation associated with the experience; summary of how the new product continues to be appropriate for the protection of the public health	Four years from the date of distribution of the last batch of each product subject to this order
Correspondence with FDA	Correspondence with FDA pertaining to each authorized product	Four years from the date of distribution of the last batch of each product subject to this order
Study data	Nonclinical or clinical study documentation including: ▪ Source data; ▪ Study protocols (including statistical analysis plan); Amendments showing the dates and reasons for each protocol revision; ▪ Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals; ▪ Informed consent forms; ▪ Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC; ▪ Investigator financial disclosure statements; ▪ Progress reports; Monitoring reports; ▪ Adverse experience reports; ▪ Case report forms/subject diaries/medical records/laboratory reports; ▪ Subject data line listings/observations records; ▪ Test article accountability records;	Four years from the date of distribution of the last batch of each product subject to this order

	▪ Study results/protocol summaries/study reports; and ▪ Certifications and amendments to certifications	

The following records must be retained on a rolling basis, that is, for a period of not less than four years from the date of distribution of *each batch of each product* subject to this order or four years from the date of initial dissemination of materials to the public, as specified below. These records must be legible, in English, and available for inspection and copying by officers or employees duly designated by the Secretary, upon request.

Type of Record	**Description**	**Retention Period**
Manufacturing records	Records pertaining to the manufacture, in process and release testing, production process (including any changes to the process, facility, or controls), packaging, storage, and stability monitoring and testing (including protocol and results). Records and reports of all manufacturing deviations, investigations, and corrective and preventive actions including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding and distribution; and any deviation that may affect the characteristics of each final product.[9]	Four years from the date of distribution of each batch of each product subject to this order
Sales and/or distribution records	A list of distributors and retailers of the products, including brick-and-mortar, and digital (including internet/online, and mobile); Any available information (not to include personally identifiable information) about product purchasers, such as purchasers' demographics (e.g., age, gender, race/ethnicity, geographic region) and previous or current use of other tobacco products (i.e., dual use); Policies and procedures regarding restrictions on youth-access to the products, including purchaser age and identity verification processes.	Four years from the date of distribution of each batch of each product subject to this order

[9] For products that have been distributed, if a deviation occurs that you determine presents a reasonable probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in tobacco products on the market that would cause serious, adverse health consequences or death you are required to report the deviation to FDA within 15 calendar days of identification.

Complaints	Records pertaining to any and all complaints associated with the tobacco product(s) that is/are the subject of this order(s). Such records may also include analysis of those complaints.	Four years from the date of distribution of each batch of each product subject to this order
Health hazard analyses	Health hazard analyses, if performed voluntarily or directed by FDA	Four years from the date of distribution of each batch of each product subject to this order
Labeling	Specimens of all labeling (including all labeling variations, such as those reflecting different required warnings), labels, inserts/onserts, instructions, and other accompanying information	Four years from the date of dissemination to the public
Advertising marketing and promotional materials and plans	Copies of all advertising, marketing and/or promotional materials, published, disseminated to consumers, or for use in engaging or communicating with consumers Copies of all advertising and marketing plans including strategic creative briefs and paid media plans, by channel and by product, and the details, dollar amount(s) and flighting of such plans, by channel and by product, including any: ▪ Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys; ▪ Targeting of specific adult audiences by age-range(s), including young adult audiences, ages 18-24, and other demographic and psychographic characteristics that reflect your intended target audience(s), how the target audience(s) were defined, and the insights used to develop the target audience profiles(s) and the source of such insights; ▪ Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and promotion; ▪ Use of owned, earned, shared/social, and/or paid media to create labeling for, advertise, market, and/or promote the products;	Four years from the date of dissemination to the public

	▪ Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products; ▪ Consumer engagements – whether conducted by you, on your behalf, or at your directions - including events at which the products will be demonstrated and/or; ▪ Use of public relations outreach to create labeling for, advertise, market, and/or promote the products. Copies of all records pertaining to media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), and all post-launch delivery-verification reports submitted to you from an accredited source, by channel, by product, and by audience demographics. Policies and procedures for real-time digital media monitoring to identify, correct, and prevent any delivery of advertising impressions to youth, ages 17 years and under, including documentation of such monitoring activities and implementation of corrective and preventive measures.	
Formative consumer research	Copies of any formative research studies conducted among any audiences, in the formation of the labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing.	Four years from the date of dissemination to the public
Consumer Evaluation Research	Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of the labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing	Four years from the date of dissemination to the public
Contractual agreements	Copies of any contractual agreements regarding the creation and/or dissemination of the products' labeling, advertising, marketing, and/or promotional materials,	Four years from the date of dissemination to the public

	including, for example in print media, online or through digital platforms (e.g., social media and mobile applications), such as influencers, bloggers, and ambassadors, on your behalf, or at your direction.	

4.3.2. Periodic Reporting

Per section 910(f) of the FD&C Act, these orders requires that you submit periodic reports every six months to FDA once during the month of June of each year and once during the month of December of each year, beginning June 2020, to help FDA determine whether continued marketing of each new tobacco product is appropriate for the protection of public health or whether there is or may be grounds for withdrawing or temporarily suspending such order. For the 6-month reporting period, the report must include:

1. A single submission with a cover letter that includes the following subject line: **PERIODIC REPORT for STN PM0000491 and PM0000492**. The cover letter should include the STN(s) and corresponding tobacco product name(s), applicant name, date of report, and reporting period.

2. All final printed labeling (including all variations, such as those reflecting different required warnings) not previously submitted (e.g., if previously submitted under section 905(i) or previously submitted at the last reporting period and no changes were made, please list the date and manner of submission), including the date the labeling was first disseminated and the date when the labeling was discontinued, and a description of all changes to the labeling. The labeling must include all the panels and be presented in the actual size and color with legible text. The labeling must include labels, inserts/onserts, instructions, and any other accompanying information or materials for the products.

3. All final full-color advertising, marketing, and/or promotional materials, published, disseminated to consumers, or for use in engaging or communicating with consumers not previously submitted (e.g., if previously submitted under 905(i) or previously submitted at the last reporting period and no changes were made, list the date and manner of submission), along with the original date such materials were first disseminated and the date they were discontinued, and a description of all changes to the materials. The materials must be legible, include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5” x 11” piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the advertisement does not allow for text to be read easily, the complete text may be provided separately and clearly referenced. Digital media, such as videos must be submitted in a format that FDA is able to open and review.

Per section 910(f) of the FD&C Act, these orders require that you submit the following postmarket reports to FDA on an annual basis, beginning November 2020, to help FDA determine whether continued marketing of each new tobacco product is appropriate for the protection of public health or whether there is or may be grounds for withdrawing or temporarily suspending such order. For the 12-month reporting period, the report must include:

1. A single submission with a cover letter that includes the following subject line: **PERIODIC REPORT for STN PM0000491 and PM0000492**. The cover letter should include the STN(s) and

corresponding tobacco product name(s), applicant name, date of report, reporting period, and marketing status outside the United States.

2. A summary of how the new product continues to be appropriate for the protection of the public health, including:

    a. A status report of ongoing studies and a summary of completed studies about the product conducted by, or on behalf of, the applicant;
    b. A summary of significant findings on publications not previously reported, with copies of the full articles included. Any new scientific data (published or otherwise) on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and use by youth and young adults must also be reported;
    c. All serious or unexpected adverse experiences reported to you, including a listing and analysis (accompanied by a statement of any changes to the reference risk information and a summary of important risks, including the nature, frequency, and potential risk factors)
    d. A summary of sales and distribution of the new product, including total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops);
    e. Data on product purchasers. Report any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results must be broken down by purchaser demographics (e.g., age, gender, and race/ethnicity, geographic location) and must not include personally identifiable information. Also, any change in the intended target market for the product should be reported. The data described above may include sales data and post-marketing analyses.

3. A summary of the implementation and effectiveness of your policies and procedures regarding verification of the age and identity of purchasers of the products.

4. A summary of the implementation and effectiveness of your policies and procedures regarding restrictions on youth access to the products.

5. A description of each change made to the manufacturing, facilities or controls during the reporting period, including:

    a. A comparison of each change to what was described in the PMTAs;
    b. The rationale for making each change;
    c. A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of the tobacco product; and the basis for concluding that each change did not result in any modification to the final product. Modifications to any component or part of the previously authorized tobacco product would render the modified tobacco product a new product, for which premarket authorization is required. These modifications should not be provided in a periodic report.

6. A summary of any stability monitoring, and testing of the Moonlight® products, including the monitoring and testing protocol(s) (including batch/lot sampling) and results.

7. A summary of all formative consumer research studies conducted– whether by you, on your behalf, or at your direction - among any audiences, in the formation of new labeling, advertising, marketing and/or promotional materials, not previously submitted, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions and behaviors toward using the products, and including the findings or these studies and copies of the stimuli used in testing.

8. A summary of all consumer evaluation research studies conducted – whether by you, on your behalf, or at your direction – among any audiences, not previously submitted, to determine the effectiveness of labeling, advertising, marketing and/or promotional materials and shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including the findings of these studies and copies of the stimuli used in testing.

9. A summary of the creation and dissemination of the products' labeling, advertising, marketing, and/or promotional materials – whether conducted by you, on your behalf, or at your direction – including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities.

10. A description of the implementation of all advertising and marketing plans not previously submitted, including strategic creative briefs and paid media plans– whether conducted by you, on your behalf, or at your direction - by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including a description of any:
    a. Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;
    b. Targeting of specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and psychographic characteristics that reflect the intended target audience, including how the target audience(s) are defined and the insights used to develop the target audience profiles(s), including the source of such insights;
    c. Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
    d. Use of owned, earned, shared/social, and/or paid media to create labeling for, advertise, market, and/or promote the products;
    e. Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
    f. Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated; and/or
    g. Use of public-relations outreach to create labeling for, advertise, market, and/or promote the products; including the original date such plans were first used and the date they were discontinued, and a description of all changes to such plans since the last periodic report, by channel and by product.

11. An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a

breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under), not previously submitted. This analysis must be verified against post-launch delivery-verification reports submitted to you from an accredited source.

12. A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to youth, ages 17 and under, and including a summary of implementation of any corrective and preventive measures, not previously submitted.

Serious Adverse Experiences Reporting

Under section 910(f) of the FD&C Act, these orders require that you 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 each new tobacco product **within 15 calendar days** after the report is received by you. These experiences may become known to you through a customer complaint, request, or suggestion made as a result of an adverse experience, a manufacturing deviation analysis, tobacco product defect, or failure reported to you; or identified in the literature or media. Your information should be submitted with a cover letter that includes the following subject line: **SERIOUS ADVERSE EXPERIENCE REPORT for STN PM0000491 and PM0000492**.

For purposes of reporting under this order, 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 in 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 reporting under these orders, 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 each tobacco product as described in the PMTA 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 persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

4.3.3. Notifications

Under sections 910(c)(1)(B) and 910(f) of the FD&C Act, this order also requires that for the first six months after the date of your marketing granted orders you provide FDA a 30-day notification for all labeling, advertising, marketing, and/or promotional materials for which you plan on disseminating to the public. These notifications are not for pre-approval but are required so that FDA can have timely access to your marketing plans and materials, and if needed, provide you advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and, on the finding, that continued marketing of your products is appropriate for the protection of the public health. You may begin disseminating the materials 30 days after providing notification to FDA. This notification must be received by FDA **at least 30 days** prior to dissemination, which includes but is not limited to the publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials.

- Full-color copies of all such labeling, advertising, marketing, and/or promotional materials for the products. The materials must be legible, include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5” x 11” piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read all lettering clearly. If resizing the advertisement does not allow for text to be read easily, the complete text may be provided separately and clearly referenced.

- All advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the details, dollar amount(s) and flighting of such plans, by channel and by product, including any plans to:

    - Use competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;
    - Target specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and psychographic characteristics that reflect your intended target audience, including how the target audience(s) are defined and the insights used to develop the target audience profile(s);
    - Restrict youth-access and limit youth-exposure to the products’ labeling, advertising, marketing, and/or promotion;
    - Use owned, earned, shared/social, and/or paid media to create labeling for, advertise, market, and/or promote the products;
    - Use partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
    - Conduct any consumer engagements – whether by you, on your behalf, or at your direction – including events at which the products will be demonstrated; and/or
    - Use public-relations outreach to create labeling for, advertise, market, and/or promote the products – including the original date such plans were first used and the date they were discontinued, and a description of all changes to such plans since the last periodic report, by channel and by product.

4.3.4. Marketing Requirements

Under section 910(c)(1)(B) of the FD&C Act, this order requires:

- For any **digital sales** – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, to prevent the sale of the products to individuals who are under the federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in your **owned digital properties** (e.g., your company-owned, consumer-directed, product-branded website(s) and/or mobile applications) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare consumer information against independent, competent, and reliable data sources, such as public records, at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in any **shared digital properties** (e.g., your product-branded social media accounts, pages and associated content; content promoting your products on your behalf disseminated through another entity's social media accounts) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of the available site-, platform- and content- (e.g., post, video) specific age-restriction controls (e.g., age-restrict an entire product-branded account and all associated content disseminated through such account; ensure age-restriction of a specific video disseminated by an influencer promoting the products on your behalf through the influencer's account), at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product(s) running on another company's website; paid advertising for the product(s) running in social media; paid distribution of influencer content) – whether conducted by you, on your behalf, or at your direction:
  - Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products. Such targeting must use only first- and/or second-party age-verified data, where:

    - "First-party" age-verified data is data owned by you (e.g., your customer registration data collected via site traffic to your company-owned website; data you use in direct marketing to your adult smoking customers) that you have age-verified through independent, competent, and reliable data sources; and

- "Second-party" age-verified data is first-party data owned and age-verified by another competent and reliable entity (e.g., another company's first-party user registration data) to which you have access. Such data must be age-verified by the second party.

- "First-party" and "second-party" data does not include data obtained from data aggregators who categorize consumers based on trackable activities and inferred interests (e.g., internet search terms, video interactions, browsing history, purchasing behaviors) to create demographic and psychographic profiles marketers may use to enhance audience targeting. Such data is not considered age-verified and can only be used in combination with first- and/or second-party age-verified data.

- Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies (e.g., using an embedded tracking pixel in all digital advertising) – whether conducted by you, on your behalf, or at your direction – to **track and measure actual delivery of all advertising impressions**, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). Such monitoring requires real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to youth, ages 17 and under. Such monitoring also requires post-launch delivery verification reports be submitted to you from an accredited source.

- For any use of **partners, influencers, bloggers, and/or brand ambassadors** to create labeling for, advertise, market, and/or promote the products – whether conducted by you, on your behalf, or at your direction – disclose to consumers or viewers, via the use of statements such as "sponsored by [firm name]" in such labeling, advertising, marketing, and/or promotional materials, any relationships between you and entities that create labeling for, advertise, market, and/or promote the products, on your behalf, or at your direction.

At any time, FDA may request that you provide any of the documents described in Appendix D. In addition, under section 704 of the FD&C Act, FDA may inspect your establishment(s) and request to inspect any record(s) described in Appendix D.

If you discontinue the manufacture, preparation, compounding or processing for commercial distribution of these tobacco products and later decide to reintroduce the products into the market, please contact the Office of Science prior to reintroduction.

You may be eligible to submit a supplemental PMTA for modification(s) made to tobacco products that received marketing granted orders, by cross-referencing content in the PMTA and postmarket reports for the original tobacco products subject of this letter. Applicants that have questions about whether it would be appropriate to submit a supplemental PMTA for modification(s) they are seeking to implement should contact their Regulatory Health Project Manager (RHPM) within the Office of Science for more information.

5. ACRONYMS

1-HOP	1-hydroxypyrene
2R4F	reference cigarette
3-HMPA	3-hydroxypropylmercapturic acid
8-iso-PGF2α	(Z)-7-[1R,2R, 3R,5S]-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoicacid
AUC_{0-180}	area under the nicotine concentration-time curve
a_w	water activity
BCP	Behavioral and Clinical Pharmacology
BIMO	Bioresearch Monitoring
BIOSIS	Biological Abstracts
BOE	biomarkers of exposure
BOPH	biomarkers of potential harm
CAS number	Chemical Abstracts Service number
CDC	Centers for Disease Control and Prevention
CI	Canadian Intense smoking regimen
C_{max}	maximum measured plasma nicotine concentration
CO	carbon monoxide
COHb	blood carboxyhemoglobin
CPD	cigarettes per day
CTP	Center for Tobacco Products
DPAL	Division of Promotion, Advertising, and Labeling
DPF	Denier Per Filament
ENDS	electronic nicotine delivery systems
FCLAA	Federal Cigarette Labeling and Advertising Act
FD&C Act	Federal Food Drug and Cosmetic Act
FDA	Food and Drug Administration
FDA50	study that characterized 50 cigarettes in 2011
FOIA	Freedom of Information Act
FONSI	finding of no significant impact
FTCD	Fagerström Test for Cigarette Dependence
FTND	Fagerström Test for Nicotine Dependence
HPHC	harmful and potentially harmful constituents
hs-CRP	high-sensitivity C-reactive protein
ISO	International Organization for Standardization machine smoking regimen
ITT	intent-to-treat population
K_{el}	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration-time curve of the controlled/uncontrolled use condition
LNC	low nicotine content
M	mean
MNWS-R	Minnesota Nicotine Withdrawal Scale - Revised
MRTP	Modified Risk Tobacco Product
MSS	mainstream smoke
N/A	not applicable
N/P	not provided

NCI	National Cancer Institute
NDSS	Nicotine Dependence Syndrome Scale
NIDA	National Institute on Drug Abuse
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNC	Normal Nicotine Content
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	n-nitrosonornicotine
NRC	Nicotine Research Cigarettes
NRT	nicotine replacement therapy
OCE	Office of Compliance and Enforcement
OS	Office of Science
PGEM	prostaglandin E2 metabolite
PheT	phenanthrene tetraol
PK	pharmacokinetic
PMTA	premarket tobacco application
PP	per protocol population
QPTase	quinolinic acid phosphoribosyltransferase
QRA	quantitative risk assessment
QSU-Brief	Brief Questionnaire of Smoking Urges
RH	relative humidity
RIM	random iterative method
RSD	relative standard deviation
SAE	serious adverse experience
SD	Standard Deviation
SDA	specially denatured alcohol
SGR	Surgeon General's Report
SHS	second hand smoke
SIDS	sudden infant death syndrome
(b)(4)	(b)(4)
S-PMA	S-phenylmercapturic acid
SRNT	Society for Research on Nicotine and Tobacco
STL	Southeast Tobacco Laboratory
STN	Submission Tracking Number
T1/2	apparent first-order terminal nicotine elimination half-life
t-con	teleconference
THS	thirdhand smoke
Tmax	time of the maximum measured plasma nicotine concentration
TNCO	tar, nicotine, and carbon monoxide
TNE	total nicotine equivalent
TOST	two one-sided tests
TPL	Technical Project Lead
TPMF	Tobacco Product Master File
TSNA	tobacco-specific nitrosamines
UB-NNC	Usual Brand- Normal Nicotine Content
VAS	visual analog scales
VLNC	Very low nicotine content
WISDM	Wisconsin Inventory of Smoking Dependence Motives

6. REFERENCES

Addicott, M. A., Froeliger, B., Kozink, R. V., Van Wert, D. M., Westman, E. C., Rose, J. E., & McClernon, F. J. (2014). Nicotine and non-nicotine smoking factors differentially modulate craving, withdrawal and cerebral blood flow as measured with arterial spin labeling. *Neuropsychopharmacology, 39*(12), 2750-2759. doi:10.1038/npp.2014.108

Barrett, S. P. (2010). The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behavioral Pharmacology, 21*(2), 144-152. doi:10.1097/FBP.0b013e328337be68

Barrett, S. P., & Darredeau, C. (2012). The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers. *Behavioral Pharmacology, 23*(3), 221-227. doi:10.1097/FBP.0b013e328353431c

Benowitz, N. L., Dains, K. M., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D., & Jacob, P., 3rd. (2012). Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiology, Biomarkers & Prevention, 21*(5), 761-769. doi:10.1158/1055-9965.epi-11-0644

Benowitz, N. L., Nardone, N., Dains, K. M., Hall, S. M., Stewart, S., Dempsey, D., & Jacob, P., 3rd. (2015). Effect of reducing the nicotine content of cigarettes on cigarette smoking behavior and tobacco smoke toxicant exposure: 2-year follow up. *Addiction, 110*(10), 1667-1675. doi:10.1111/add.12978

Brunnemann, K. D., Prokopczyk, B., Djordjevic, M. V., & Hoffmann, D. (1996). Formation and analysis of tobacco-specific N-nitrosamines. *Critical Reviews in Toxicology, 26*(2), 121-137. doi:10.3109/10408449609017926

Buchhalter, A. R., Acosta, M. C., Evans, S. E., Breland, A. B., & Eissenberg, T. (2005). Tobacco abstinence symptom suppression: The role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction, 100*(4), 550-559. doi:10.1111/j.1360-0443.2005.01030.x

Carter, L. P., & Griffiths, R. R. (2009). Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug and alcohol dependence, 105 Suppl 1*, S14-25. doi:10.1016/j.drugalcdep.2009.04.003

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., Miller, M. E., Tidey, J. W., Diguiseppi, G., Denlinger-Apte, R., & Colby, S. M. (2019). The impact of nicotine dose on the reinforcing value of cigarettes in adolescents. *Tob Regul Sci, 5*(2), 105-114. doi:10.18001/TRS.5.2.2

Castrucci, B. C., Gerlach, K. K., Kaufman, N. J., & Orleans, C. T. (2002). Adolescents' acquisition of cigarettes through noncommercial sources. *J Adolesc Health, 31*(4), 322-326.

(b)(4)

Cobb, C. O., Weaver, M. F., & Eissenberg, T. (2010). Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tobbaco Control, 19*(5), 367-373. doi:10.1136/tc.2008.028993

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, 41*(3), 185-227. doi:10.1016/j.yrtph.2004.12.002

Cummings, K. M., Sciandra, E., Pechacek, T. F., Orlandi, M., & Lynn, W. R. (1992). Where teenagers get their cigarettes: A survey of the purchasing habits of 13-16 year olds in 12 US communities. . *Tob Control, 1*(4), 264-267. Retrieved from http://www.jstor.org/stable/20206836

Dallery, J., Houtsmuller, E. J., Pickworth, W. B., & Stitzer, M. L. (2003). Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking. *Psychopharmacology (Berl), 165*(2), 172-180. doi:10.1007/s00213-002-1242-8

Davis, D. R., Miller, M. E., Streck, J. M., Bergeria, C. L., Sigmon, S. C., Tidey, J. W., . . . Higgins, S. T. (2019). Response to Reduced Nicotine Content in Vulnerable Populations: Effect of Menthol Status. *Tob Regul Sci, 5*(2), 135-142. doi:10.18001/TRS.5.2.5

Delnevo, C. D., Gundersen, D. A., Hrywna, M., Echeverria, S. E., & Steinberg, M. B. (2011). Smoking-cessation prevalence among U.S. smokers of menthol versus non-menthol cigarettes. *American Journal of Preventive Medicine, 41*(4), 357-365. doi:10.1016/j.amepre.2011.06.039

Denlinger-Apte, R., Kotlyar, M., Koopmeiners, J., Tidey, J., Luo, X., Jensen, J., . . . Hatsukami, D. (2019). *The effects of menthol flavoring on smoking behavior and biomarkers of exposure in smokers using very low nicotine content cigarettes for 20 weeks: Podium presentation February 21, 2019*. Paper presented at the Society for Research on Nicotine and Tobacco.

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. *Tob Regul Sci, 2*(2), 186-203. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5870904/pdf/nihms946129.pdf

Ding, Y. S., Yan, X. J., Jain, R. B., Lopp, E., Tavakoli, A., Polzin, G. M., . . . Watson, C. H. (2006). Determination of 14 polycyclic aromatic hydrocarbons in mainstream smoke from U.S. brand and non-U.S. brand cigarettes. *Environmental Science & Technology, 40*(4), 1133-1138. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16572766
http://pubs.acs.org/doi/pdfplus/10.1021/es0517320

Ding, Y. S., Zhang, L., Jain, R. B., Jain, N., Wang, R. Y., Ashley, D. L., & Watson, C. H. (2008). Levels of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. *Cancer Epidemiology Biomarkers & Prevention, 17*(12), 3366-3371.

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., Houtsmuller, E., & Stitzer, M. L. (2007). Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction, 102*(2), 324-334. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1360-0443.2006.01670.x

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

Eid, N. C., Fant, R. V., Moolchan, E. T., & Pickworth, W. B. (2005). Placebo cigarettes in a spaced smoking paradigm. *Pharmacology Biochemistry and Behavior, 81*(1), 158-164. doi:10.1016/j.pbb.2005.03.007

Faseru, B., Nollen, N. L., Mayo, M. S., Krebill, R., Choi, W. S., Benowitz, N. L., . . . Sanderson Cox, L. (2013). Predictors of cessation in African American light smokers enrolled in a bupropion clinical trial. *Addict Behav, 38*(3), 1796-1803. doi:10.1016/j.addbeh.2012.11.010

Faulkner, P., Ghahremani, D. G., Tyndale, R. F., Cox, C. M., Kazanjian, A. S., Paterson, N., . . . London, E. D. (2017). Reduced-nicotine cigarettes in young smokers: impact of nicotine metabolism on nicotine dose effects. *Neuropsychopharmacology, 42*(8), 1610-1618. doi:10.1038/npp.2017.18

Faulkner, P., Petersen, N., Ghahremani, D. G., Cox, C. M., Tyndale, R. F., Hellemann, G. S., & London, E. D. (2018). Sex differences in tobacco withdrawal and responses to smoking reduced-nicotine

cigarettes in young smokers. *Psychopharmacology (Berl), 235*(1), 193-202. doi:10.1007/s00213-017-4755-x

Godtfredsen, N. S., Holst, C., Prescott, E., Vestbo, J., & Osler, M. (2002). Smoking reduction, smoking cessation, and mortality: A 16-year follow-up of 19,732 men and women from the copenhagen centre for prospective population studies. *American Journal of Epidemiology, 156*(11), 994-1001. doi:10.1093/aje/kwf150

Hammond, D., & O'Connor, R. J. (2014). Reduced nicotine cigarettes: smoking behavior and biomarkers of exposure among smokers not intending to quit. *Cancer Epidemiology, Biomarkers & Prevention, 23*(10), 2032-2040. doi:10.1158/1055-9965.epi-13-0957

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., Hertsgaard, L. A., Vogel, R. I., Jensen, J. A., Murphy, S. E., Hecht, S. S., . . . Allen, S. S. (2013). Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiology, Biomarkers & Prevention, 22*(6), 1015-1024. doi:10.1158/1055-9965.EPI-12-1439

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., . . . al'Absi, M. (2017). Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction, 112*(1), 156-167. doi:10.1111/add.13603

Hatsukami, D. K., Luo, X., Heskin, A. K., Tang, M. K., Carmella, S. G., Jensen, J., . . . Hecht, S. S. (2019). Effects of immediate versus gradual nicotine reduction in cigarettes on biomarkers of biological effects. *Addiction*. doi:10.1111/add.14695

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. *JAMA, 320*(9), 880-891. doi:10.1001/jama.2018.11473

Hersey, J. C., Ng, S. W., Nonnemaker, J. M., Mowery, P., Thomas, K. Y., Vilsaint, M. C., . . . Haviland, M. L. (2006). Are menthol cigarettes a starter product for youth? *Nicotine & Tobacco Research, 8*(3), 403-413. doi:10.1080/14622200600670389

Higgins, S. T., Heil, S. H., Sigmon, S. C., Tidey, J. W., Gaalema, D. E., Stitzer, M. L., . . . Pacek, L. R. (2017). Response to varying the nicotine content of cigarettes in vulnerable populations: An initial experimental examination of acute effects. *Psychopharmacology (Berl), 234*(1), 89-98. doi:10.1007/s00213-016-4438-z

Hoffmann, D., Djordjevic, M. V., & Hoffmann, I. (1997). The changing cigarette. *Preventive Medicine, 26*(4), 427-434. doi:10.1006/pmed.1997.0183

Hoffmann, D. H., & Hoffmann, I. (2001). The changing cigarette: Chemical studies and bioassays. In *National Cancer Institute: Smoking and Tobacco Control Monograph* (Vol. 13, pp. 159-191).

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.

Juliano, L. M., Donny, E. C., Houtsmuller, E. J., & Stitzer, M. L. (2006). Experimental evidence for a causal relationship between smoking lapse and relapse. *Journal of Abnormal Psychology, 115*(1), 166-173. doi:10.1037/0021-843x.115.1.166

Juliano, L. M., Fucito, L. M., & Harrell, P. T. (2011). The influence of nicotine dose and nicotine dose expectancy on the cognitive and subjective effects of cigarette smoking. *Exp Clin Psychopharmacol, 19*(2), 105-115. doi:10.1037/a0022937

Kassel, J. D., Greenstein, J. E., Evatt, D. P., Wardle, M. C., Yates, M. C., Veilleux, J. C., & Eissenberg, T. (2007). Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers. *Journal of Adolescent Health, 40*(1), 54-60. doi:10.1016/j.jadohealth.2006.08.006

Kozlowski, L. T., Mehta, N. Y., Sweeney, C. T., Schwartz, S. S., Vogler, G. P., Jarvis, M. J., & West, R. J. (1998). Filter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom, and the United States. *Tob Control, 7*(4), 369-375. doi:10.1136/tc.7.4.369

Kozlowski, L. T., & O'Connor, R. J. (2002). Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. *Tob Control, 11*(suppl 1), i40-i50. doi:10.1136/tc.11.suppl_1.i40

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. doi:https://doi.org/10.1006/pmed.2000.0680

Lenk, K. M., Toomey, T. L., Shi, Q., Erickson, D. J., & Forster, J. L. (2014). Do sources of cigarettes among adolescents vary by age over time? *J Child Adolesc Subst Abuse, 23*(2), 137-143. doi:10.1080/1067828x.2012.750972

Levy, D. T., Blackman, K., Tauras, J., Chaloupka, F. J., Villanti, A. C., Niaura, R. S., . . . Abrams, D. B. (2011). Quit attempts and quit rates among menthol and nonmenthol smokers in the United States. *American Journal of Public Health, 101*(7), 1241-1247. doi:10.2105/ajph.2011.300178

Lindsey, K. P., Bracken, B. K., Maclean, R. R., Ryan, E. T., Lukas, S. E., & Frederick, B. D. (2013). Nicotine content and abstinence state have different effects on subjective ratings of positive versus negative reinforcement from smoking. *Pharmacology Biochemistry & Behavior, 103*(4), 710-716. doi:10.1016/j.pbb.2012.11.012

Macqueen, D. A., Heckman, B. W., Blank, M. D., Janse Van Rensburg, K., Evans, D. E., & Drobes, D. J. (2012). Transient compensatory smoking in response to placebo cigarettes. *Psychopharmacology (Berl), 223*(1), 47-54. doi:10.1007/s00213-012-2685-1

McRobbie, H., Przulj, D., Smith, K. M., & 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

Mercincavage, M., Souprountchouk, V., Tang, K. Z., Dumont, R. L., Wileyto, E. P., Carmella, S. G., . . . Strasser, A. A. (2016). A randomized controlled trial of progressively reduced nicotine content cigarettes on smoking behaviors, biomarkers of exposure, and subjective ratings. *Cancer Epidemiology, Biomarkers & Prevention, 25*(7), 1125-1133. doi:10.1158/1055-9965.epi-15-1088

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. doi:10.1186/s12868-015-0173-3

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*. doi:10.1111/add.13519

Novotny, T. E., Hardin, S. N., Hovda, L. R., Novotny, D. J., McLean, M. K., & Khan, S. (2011). Tobacco and cigarette butt consumption in humans and animals. *Tob Control, 20*(Suppl 1), i17-i20. doi:10.1136/tc.2011.043489

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. *Am J Health Behav, 31*(4), 402-410. doi:10.5555/ajhb.2007.31.4.402

O'Connor, R. J., Hammond, D., McNeill, A., King, B., Kozlowski, L. T., Giovino, G. A., & Cummings, K. M. (2008). How do different cigarette design features influence the standard tar yields of popular

cigarette brands sold in different countries? *Tob Control, 17*(Suppl 1), i1-i5. doi:10.1136/tc.2006.019166

Okuyemi, K. S., Ahluwalia, J. S., Ebersole-Robinson, M., Catley, D., Mayo, M. S., & Resnicow, K. (2003). Does menthol attenuate the effect of bupropion among African American smokers? *Addiction, 98*(10), 1387-1393.

Pauwels, C. G. G. M., Klerx, W. N. M., Pennings, J. L. A., Boots, A. W., van Schooten, F. J., Opperhuizen, A., & Talhout, R. (2018). Cigarette Filter Ventilation and Smoking Protocol Influence Aldehyde Smoke Yields. *Chemical Research in Toxicology, 31*(6), 462-471. doi:10.1021/acs.chemrestox.7b00342

Perkins, K. A., & Karelitz, J. L. (2015). Sex differences in acute relief of abstinence-induced withdrawal and negative affect due to nicotine content in cigarettes. *Nicotine & Tobacco Research, 17*(4), 443-448. doi:10.1093/ntr/ntu150

Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. *Nicotine & Tobacco Research*.

Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2018). Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes differing in nicotine content. *Journal of Psychopharmacology, 32*(3), 324-331.

Pickworth, W. B., Nelson, R. A., Rohrer, M. S., Fant, R. V., & Henningfield, J. E. (1999). Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine & Tobacco Research, 1*(4), 357-364.

Pilling, L. C., Atkins, J. L., Kuchel, G. A., Ferrucci, L., & Melzer, D. (2018). Red cell distribution width and common disease onsets in 240,477 healthy volunteers followed for up to 9 years. *PLoS One, 13*(9), e0203504. doi:10.1371/journal.pone.0203504

Ramachandran, J., Rubenstein, D., Bluestein, D., & Jesty, J. (2004). Activation of platelets exposed to shear stress in the presence of smoke extracts of low-nicotine and zero-nicotine cigarettes: the protective effect of nicotine. *Nicotine & Tobacco Research, 6*(5), 835-841.

Rezaishiraz, H., Hyland, A., Mahoney, M. C., O'Connor, R. J., & Cummings, K. M. (2007). Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings? *Nicotine & Tobacco Research, 9*(11), 1139-1146. doi:10.1080/14622200701684172

Rigotti, N. A. (2018, February 6). Benefits and risks of smoking cessation. *UpToDate.* Retrieved from https://www.uptodate.com/contents/benefits-and-risks-of-smoking-cessation/print

Roemer, E., Schramke, H., Weiler, H., Buettner, A., Kausche, S., Weber, S., . . . Wittke, S. (2012). Mainstream smoke chemistry and in vitro and in vivo toxicity of the reference cigarettes 3R4F and 2R4F. *Beiträge zur Tabakforschung International/Contributions to Tobacco Research, 25*(1), 316-335. doi:https://doi.org/10.2478/cttr-2013-0912

Rose, J. E., & Behm, F. M. (2004). Effects of low nicotine content cigarettes on smoke intake. *Nicotine & Tobacco Research, 6*(2), 309-319. doi:10.1080/14622200410001676378

Rose, J. E., Salley, A., Behm, F. M., Bates, J. E., & Westman, E. C. (2010). Reinforcing effects of nicotine and non-nicotine components of cigarette smoke. *Psychopharmacology (Berl), 210*(1), 1-12. doi:10.1007/s00213-010-1810-2

Schlagintweit, H. E., & Barrett, S. P. (2016). Does acute tobacco smoking prevent cue-induced craving? *Journal of Psychopharmacology, 30*(5), 468-473. doi:10.1177/0269881116639288

Shiffman, S., Kurland, B. F., Scholl, S. M., & Mao, J. M. (2018). Nondaily smokers' changes in cigarette consumption with very low-nicotine-content cigarettes: A randomized double-blind clinical trial. *JAMA Psychiatry*.

Song, M., Benowitz, N. L., Berman, M., Brasky, T. M., Cummings, K. M., Hatsukami, D. K., . . . Shields, P. G. (2017). Cigarette filter ventilation and its relationship to increasing rates of lung adenocarcinoma. *Journal of the National Cancer Institute, 109*(12), djx075-djx075. doi:10.1093/jnci/djx075

Stephens, W. E. (2007). Dependence of tar, nicotine and carbon monoxide yields on physical parameters: implications for exposure, emissions control and monitoring. *Tob Control, 16*(3), 170-176. doi:10.1136/tc.2006.017491

Strasser, A. A., Lerman, C., Sanborn, P. M., Pickworth, W. B., & Feldman, E. A. (2007). New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug and alcohol dependence, 86*(2-3), 294-300. doi:10.1016/j.drugalcdep.2006.06.017

Sung, H., 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. doi:10.1093/ntr/ntv147

Talhout, R., Opperhuizen, A., & van Amsterdam, J. G. (2007). Role of acetaldehyde in tobacco smoke addiction. *European Neuropsychopharmacology, 17*(10), 627-636. doi:10.1016/j.euroneuro.2007.02.013

Tidey, J. W., Cassidy, R. N., & Miller, M. E. (2016). Smoking topography characteristics of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls. *Nicotine & Tobacco Research, 18*(9), 1807-1812. doi:10.1093/ntr/ntw089

Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., Swift, R. M., & Ahnallen, C. G. (2013). Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls. *Nicotine & Tobacco Research, 15*(1), 121-129. doi:10.1093/ntr/nts098

Trinidad, D. R., Perez-Stable, E. J., Messer, K., White, M. M., & Pierce, J. P. (2010). Menthol cigarettes and smoking cessation among racial/ethnic groups in the United States. *Addiction, 105 Suppl 1*, 84-94. doi:10.1111/j.1360-0443.2010.03187.x

Tverdal, A., & Bjartveit, K. (2006). Health consequences of reduced daily cigarette consumption. *Tob Control, 15*(6), 472-480. doi:10.1136/tc.2006.016246

U.S. Department of Health and Human Services. (2001). *2001 Surgeon General's Report-- Women and Smoking*. Retrieved from Rockville, MD: https://www.cdc.gov/tobacco/data_statistics/sgr/2001/complete_report/index.htm

U.S. Department of Health and Human Services. (2004). *2004 Surgeon General's Report--The Health Consequences of Smoking*. Retrieved from Rockville, MD: http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/exec-summary.pdf

U.S. Department of Health and Human Services. (2012). *Preventing tobacco use among youth and young adults: A report of the Surgeon General*. Retrieved from https://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/index.html

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

University of Kentucky. 3R4F PReliminary Analysis. Retrieved from https://ctrp.uky.edu/assets/pdf/webdocs/3R4F%20Preliminary%20Analysis.pdf

Vogel, R. I., Hertsgaard, L. A., Dermody, S. S., Luo, X., Moua, L., Allen, S., . . . Hatsukami, D. K. (2014). Sex differences in response to reduced nicotine content cigarettes. *Addictive Behaviors, 39*(7), 1197-1204. doi:10.1016/j.addbeh.2014.03.021

Wackowski, O., & Delnevo, C. D. (2007). Menthol cigarettes and indicators of tobacco dependence among adolescents. *Addictive Behaviors, 32*(9), 1964-1969. doi:10.1016/j.addbeh.2006.12.023

Walker, N., Fraser, T., Howe, C., Laugesen, M., Truman, P., Parag, V., . . . Bullen, C. (2015). Abrupt nicotine reduction as an endgame policy: A randomised trial. *Tob Control, 24*(e4), e251-257. doi:10.1136/tobaccocontrol-2014-051801

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