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I. Executive Summary

A. Background

On May 17, 2019, 22nd Century Group Inc. submitted modified risk tobacco product applications (MRTPAs) stating that it is seeking exposure modification orders under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for its VLN™ King and VLN™ Menthol King combustible cigarettes, which were received by FDA on May 20, 2019.

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

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

B. Exposure Modification Order Request

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

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

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

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

- Claim #4: “VLN™ cigarettes are substantially lower in nicotine content than any other cigarettes currently available to smokers in the United States. VLN™ cigarette contain an average of just 0.27 mg of nicotine.”

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

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

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

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

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

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

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

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

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

- Such an order would be appropriate to promote the public health;

- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a

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

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

- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and

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

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

- The magnitude of overall reductions in exposure to the substance or substances that are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;

- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;

- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and

- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(B) of the FD&C Act).

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

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

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

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

- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and

- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

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

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

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

C. Summary of findings

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

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

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

the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. Currently, "scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards set forth ..." in 911(g)(1) because issuance of an order under 911(g)(1) requires a demonstration that the product as actually used by consumers will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" and "benefit the health of the population as a whole". The applicant did not make such a demonstration for these products. There are outstanding questions about the manner in which consumers will use VLN, and if individual tobacco users use VLN cigarettes in the same frequency and manner as conventional cigarettes, they will not significantly reduce harm and their risk of tobacco-related disease. However, as described in this review, cigarette smokers' use of VLN cigarettes is likely to lead to reduced nicotine consumption, indicators of nicotine dependence, and likely overall cigarette consumption, which reasonably likely lead to reduced morbidity or mortality among these users, compared with continuing to smoke conventional cigarettes.

Bridging from SPECTRUM NRC102/103

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

Reduced exposure claim substantiation

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

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

- Claim #1: "95% less nicotine"

- Claim #4: “VLN™ cigarettes are substantially lower in nicotine content than any other cigarettes currently available to smokers in the United States. VLN™ cigarette contain an average of just 0.27 mg of nicotine.”

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Individual health impact among tobacco users

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

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

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

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

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

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

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

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

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

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

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

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

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

Population health impact

Regarding population health impact, the available scientific evidence demonstrates that the issuance of an exposure modification order for the proposed MRTPs would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. The social science review found that after viewing product labels with the exposure reduction claims, many current smokers were interested in VLN™ cigarettes (mean intentions were above the midpoint of the scale), and smokers had significantly higher intentions to purchase the proposed MRTPs compared to Marlboro Gold cigarettes. Current smokers also reported substantially higher intentions to use VLN™ cigarettes on a regular, ongoing basis compared to Marlboro Gold™. Additionally, adult never smokers and former smokers had low intentions to buy and use VLN™ (mean intentions were near the bottom of the scale), and these intentions were similar to or slightly higher than their intentions to buy and use Marlboro Gold.™

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

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

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

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

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

Under section 911(g)(2)(A)(iii) of the FD&C Act, to issue an exposure modification order, FDA must find "that scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards set forth in [section 911(g)(1)]." The available evidence is not sufficient to conclude that the applicant has demonstrated that the products, as actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users" and "benefit the health of the population as a whole." There are no long-term epidemiological studies on cigarette consumption among VLN™ cigarette smokers and the CPD consumption evidence provided by the applicant was based on clinical studies where NNC smokers, with no intention to reduce their nicotine consumption nor quit smoking, were instructed to switch to use VLN™ cigarettes. It is not clear how well CPD findings from clinical

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

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

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

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

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

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

II. Regulatory Information

A. Regulatory History

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

- May 20, 2019: original MRTPAs.
- May 23, 2019: an amendment containing updates to Section V. Labels, Labeling, and Advertising.
- June 25, 2019: an amendment containing 12-month storage stability and water activity study results.
- July 18, 2019: an amendment containing a new, 6-week clinical study sponsored by the applicant involving 140 subjects evaluating use behavior and biomarkers.
- August 7, 2019: an amendment containing additional medical information on the serious adverse event experience in the 6-week clinical study.
- August 28, 2019: an amendment containing clarification on the stimuli participants viewed in the study's "VLN™ control" condition in the quantitative consumer perception M/A/R/C Research study.