22nd Century Group, Inc.

May 13, 2019

SUBMITTED VIA CTP PORTAL UPLOAD ONLY
Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)

Re: Modified Risk Tobacco Application (MRTPA) for VLN™ King and VLN™ Menthol King Cigarettes

Dear Sir or Madam,

22nd Century Group, Inc. (the Company, 22nd Century, or XXII) is submitting this Modified Risk Product Application (MRTPA) under Section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requesting Exposure Modification Orders for two VLN™ cigarette products for claims regarding reduced exposure to nicotine. A Premarket Tobacco Application (PMTA) for the same two products was submitted on December 4, 2018, intending to satisfy applicable premarket review requirements under section 910 of the FD&C Act. The information in this MRTPA demonstrates that the requested order would be appropriate to promote the public health. It is critical for consumers to understand the basic nature of the products through disclosure of their very low nicotine content; therefore, at this time, Company does not intend to make VLN™ cigarettes available to consumers in the United States in the absence of an MRTP order.

VLN™ cigarettes are identical to conventional cigarettes except that they contain VLN™ tobacco. VLN™ tobacco is tobacco that has been modified/selected to contain less nicotine than conventional tobacco. Specifically, VLN™ tobacco contains a target level of 0.5 mg of nicotine per gram of tobacco (at least 95% less nicotine than conventional tobacco used in the top 100 cigarette brands on the market in the United States).

Section 911(g)(2)(A) of the FD&C Act specifies information that the applicant must demonstrate in order for the FDA to issue an exposure modification order. The table below identifies the demonstrated information and its location in the application:

Section 911(g)(2)(A) Requirement	**Principal Data Demonstrating Requirement**	**Sections of the Application**
The magnitude of 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;	>95% reduction in nicotine content in cigarette >95% reduction in smoke yield of nicotine > 95% reduction in plasma nicotine >95% reduction in total nicotine equivalents in urine	VIII. Scientific Studies and Analyses B. Product Analysis 1. Nicotine in Tobacco VIII. Scientific Studies and Analyses B. Product Analysis 2. Nicotine in Smoke and HPHC Analysis VIII. Scientific Studies and Analyses D. Clinical Studies
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;	The products have substantially similar HPHC levels as the market leading brands with specific reductions in select constituents. Quantitative risk assessments suggest no increased risks as compared to conventional cigarettes. Modeling study predicts conventional cigarette smokers who switch to VLN™ cigarettes will avoid about 340,000 smoking-attributable deaths and add about 8.05 million life-years to their lives by the year 2100.	VIII. Scientific Studies and Analyses B. Product Analysis 2. Nicotine in Smoke and HPHC Analysis VIII. Scientific Studies and Analyses B. Product Analysis 3. Quantitative Risk Assessment VIII. Scientific Studies and Analyses F. Effect on the Population as a Whole
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	Perception studies show that the consumers understand the product concept. Consumers perceive the health risks of VLN™ cigarettes to be similar to conventional cigarettes.	VIII. Scientific Studies and Analyses E. Effect on Consumer Understanding and Perceptions

harmful or presents, or has been demonstrated to present, less of a risk of disease than one or more other commercially marketed tobacco products		
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	Perception studies show never smokers and former smokers have no interest in the product. A modeling study predicts conventional cigarette smokers who switch to VLN™ cigarettes will avoid about 340,000 smoking-attributable deaths and add about 8.05 million life-years to their lives by the year 2100.	VIII. Scientific Studies and Analyses E. Effect on Consumer Understanding and Perceptions VIII. Scientific Studies and Analyses F. Effect on the Population as a Whole

Section 911(d) of the FD&C Act specifies information that the applicant must include in the MRTPA. The table below identifies the information being provided and its location in the Application:

Section 911(d) Requirements	**Section of Application**
A description of the proposed product and any proposed advertising and labeling	IV. Descriptive Information A. Product Description V. Labels, Labeling, and Advertising
The conditions for using the product	IV. Descriptive Information D. Conditions for Using the Product
The formulation of the product	IV. Descriptive Information B. Product Formulation
Sample product labels and labeling	V. Labels, Labeling, and Advertising
All documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health	VIII. Scientific Studies and Analyses B. Product Analysis VIII. Scientific Studies and Analyses C. Nonclinical Studies VIII. Scientific Studies and Analyses D. Clinical Studies IX. All Documents

Data and information on how consumers actually use the product.	IV. Descriptive Information E. How Consumers Actually Use the Product

This MRTPA contains copies of published studies, unpublished new studies, and studies currently in the final stages of completion. The data for the following study is referenced in the application, however the final report is not yet available:

A Study to Assess Changes in Cigarette Consumption During a Switch to Very Low Nicotine Cigarettes.
ClinicalTrials.gov Identifier: NCT03571724
Sponsor: 22nd Century Group, Inc.
Collaborator: Celerion

The final report on this study will be submitted in an amendment to this MRTPA as soon as it becomes available.

There are a substantial number of ongoing studies listed on clinicaltrials.gov using SPECTRUM® cigarettes identical to the subject products. These studies are not being conducted on behalf of XXII and XXII has no control over the study design or release of results. The results of these studies, as well as any other relevant studies, will be submitted in one or more amendments to this MRTPA as the results become publicly available.

The following information is provided in support of this MRTPA:

Applicant:

22nd Century Group, Inc.
8560 Main Street, Suite 4
Williamsville, NY 14221
Phone: (716) 270-1523
Fax: (716) 877-3064

Name of Manufacturer:

NASCO Products, LLC
321 Farmington Rd
Mocksville, NC 27028
Phone: 336-940-3769

Authorized Contact:

(b) (6)
Program Manager
22nd Century Group, Inc.
8560 Main Street, Suite 4
Williamsville, NY 14221
Email: (b) (6)
Phone: (b) (6) extension (b) (6)
Alt. Phone: (b) (6)

Product-identifying Information:

Product Names	VLN™ King	VLN ™ Menthol King
Product Category	Cigarette, Combusted, Filtered	Cigarette, Combusted, Filtered
Package Type	Hard Pack	Hard Pack
Packaging Quantity	20 per Pack	20 per Pack
Length	83 mm	83 mm
Diameter	7.9 mm	7.9 mm
Ventilation	13%	13%
Characterizing Flavor	None	Menthol

Item No. (UPC)	MRTPA Product	Package
859765005061	VLN™ King	Pack
859765005078	VLN™ King	Carton
859765005085	VLN™ King	Case
859765005092	VLN™ Menthol King	Pack
859765005108	VLN™ Menthol King	Carton
859765005115	VLN™ Menthol King	Case

List of Previous Submissions:

FDA Submission Tracking Number (STN)	*Content*	*Date*
MR0000047 and MR0000048	PMTA/MRTPA for PARE Cigarettes	December 30, 2015
MR0000047 and MR0000048 PM0000030 and PM0000031	Withdrawal Letter	January 4, 2017
MR0000047 and MR0000048	Meeting Package	June 15, 2017
MR0000047 and MR0000048	All Documents Requirement	January 25, 2018
MR0000047 and MR0000048	All Documents Requirement	February 28, 2018
MR0000047 and MR0000048	Request for Meeting	July 25, 2018
MR0000047 and MR0000048	Request for Meeting	August 30, 2018
MR0000047 and MR0000048	Revised Request for Meeting	September 28, 2018

PM0000491 and PM0000492	PMTA for VLN™ Cigarettes	December 4, 2018
MR0000140 and MR0000141	MRTPA for VLN™ Cigarettes	December 27, 2018

Type of Order Sought:

Exposure Modification Order under 911(g)(2) of the FD&C Act. The Company intends to satisfy the applicable premarket review requirements under section 910 of the FD&C Act through a PMTA submitted on December 4, 2018.

Trade Secrets or Confidential Commercial Information:

This MRTPA contains non-public, trade secret, and confidential commercial information throughout. This information belongs to the Company or it's suppliers and is exempt from public disclosure. The Company understands that the FDA is required to make this MRTPA public and in order to facilitate publication of the portions that are not trade secret or otherwise confidential commercial information, a redacted version is to be submitted by the Company identifying the portions exempt from public disclosure. In the event that any information that has been identified or designated as confidential by the Company is considered non-confidential by the FDA, the Company requests that the FDA provide pre-disclosure notice to XXII pursuant to the procedures set forth in 21 C.F.R §201.61(d) and (e).

The Company appreciates the FDA's consideration of this MRTPA and welcomes the opportunity to discuss with the FDA any questions they may have. XXII looks forward to working with the FDA to secure orders under 911(g)(2) of the FD&C Act for the subject products discussed herein and in the attached MRTPA.

Sincerely,

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Program Manager
22nd Century Group, Inc.