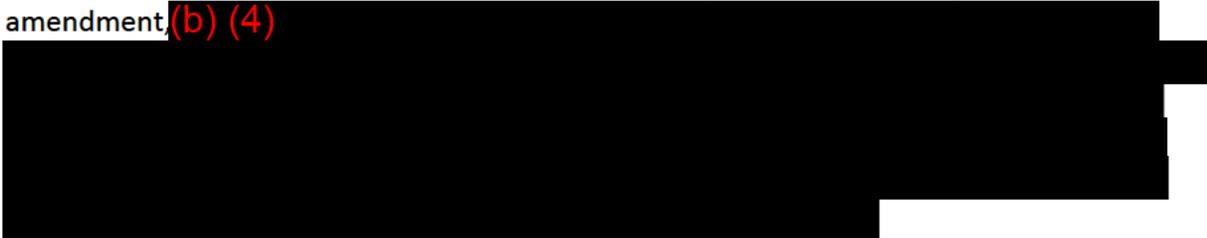


Amendment – Supporting Documentation for Section VIII.E.2 Scientific Studies and Analyses Consumer Perception

Quantitative Study to Develop VLN® Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users

This amendment provides a correction to information provided in our August 28, 2019 amendment. (b) (4)



(b) (4)



Confidentiality: A version with proposed redactions is also being submitted.

In an amendment dated August 28, 2019, 22nd Century Group, Inc. (the “Company” or “XXII”) incorrectly noted that the following files, submitted with XXII’s Modified Risk Tobacco Product Application (“MRTPA”) dated May 17, 2019, should be disregarded or withdrawn from the application:

MARC_QN_Appx_H_Stimuli_C4_VLN M - Back.jpg

MARC_QN_Appx_H_Stimuli_C4_VLN M - Combined.jpg
 MARC_QN_Appx_H_Stimuli_C4_VLN M - Front.jpg
 MARC_QN_Appx_H_Stimuli_C4_VLN R - Back.jpg
 MARC_QN_Appx_H_Stimuli_C4_VLN R - Combined.jpg
 MARC_QN_Appx_H_Stimuli_C4_VLN R - Front.jpg

In the August 28, 2019 amendment, XXII submitted replacement files. After further and subsequent review, it has been determined that the files submitted with XXII’s May 17, 2019 MRTPA, were, in fact, the correct files. These files were shown to the VLN® Control Condition (also referred to in the Study Report and Protocol as the VLN No Messaging, Control 1, and No Claims Messaging condition) in the quantitative consumer perception study, *M/A/R/C Research 2018, “Quantitative Study to Evaluate VLN Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users”*; Protocol Number: 5180080-VLN-B2; Principal Investigator: Randall Wahl. 22nd Century Group, Inc. would like the following files submitted with its August 28, 2019 amendment, to be disregarded:

VLN M - Back - Cell 4 REVISED.jpg
 VLN M - Combined - Cell 4 REVISED.jpg
 VLN M - Front - Cell 4 REVISED.jpg
 VLN R - Back - Cell 4 REVISED.jpg
 VLN R - Combined - Cell 4 REVISED.jpg
 VLN R - Front - Cell 4 REVISED.jpg

Included with this amendment are the stimuli, including 3D rotating images, that were shown to the VLN® Control Condition.

M/A/R/C® Research, LLC (“MARC”) has conducted a second review of the VLN® Control Condition. Their findings are enclosed with this letter. Below is a legend to match up the file names noted by MARC with the files in the application:

MARC Letter File Name	XXII Application File Name
VLN A - Side 1 - Bar Code.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN A - Side 1 - Bar Code.jpg
VLN A - Side 2 - SG Warning.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN A - Side 2 - SG Warning.jpg

VLN M - 3D - Cell 4.pdf	MARC_QN_Appx_H_Stimuli_C4_VLN M - 3D.pdf
VLN M - Back – Cell 4.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN M - Back.jpg
VLN M - Combined – Cell 4.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN M - Combined.jpg
VLN M - Front – Cell 4.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN M - Front
VLN R - 3D - Cell 4.pdf	MARC_QN_Appx_H_Stimuli_C4_VLN R - 3D.pdf
VLN R - Back – Cell 4.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN R - Back.jpg
VLN R - Combined – Cell 4.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN R - Combined.jpg
VLN R - Front – Cell 4.jpg	MARC_QN_Appx_H_Stimuli_C4_VLN R - Front.jpg

(b) (4) as outlined in the MRTPA guidance document, the applicant should conduct consumer studies to assess how consumers perceive the product and its associated labels, labeling, and/or marketing. “These studies should provide data regarding how consumers perceive the risks to health from using the product, and the likelihood of trying the product.” The goal of this quantitative perception study was to evaluate the VLN® product labeling to determine its impact on perceptions of the health risks and addiction risks as well as purchase and use intent in current, former, and never smokers. Various sub-groups including intention to quit in current smokers and short and long-term quitters in former smokers and potential underage individuals in never smokers were evaluated. The study design compared VLN® messages to conventional cigarette products, e-cigarettes, snuff, and NRT. At the time the study was designed, multiple possible claim statements were contemplated and included in the study. In the final application, the claims applied for in the MRTPA are “95% less nicotine” and “Helps reduce your nicotine consumption”. In the original study design, it was decided to include a branded conventional cigarette, Marlboro Gold, to provide a real reference point to the marketplace. That is, the study participant saw a real

product rather than a concept of “conventional cigarette” product as a category. The information from this cell was intended to provide a benchmark for comparison purposes. The market-leading brand was chosen. A head to head comparison would show how participants viewed VLN[®], both with and without claims, to the major comparator product and provide direct comparisons of the impact on the new product with its claims. In all cases, the response to the Marlboro Gold was consistent with the concept of conventional cigarettes. This validated the results of the overall study. Participants perceived the average health risks of VLN[®] (95% less nicotine; Helps reduce your nicotine consumption) to be slightly less than conventional cigarettes and Marlboro Gold. The perceived health risks were still relatively high and on the far left of the risk continuum (closer to conventional cigarettes on the far-left than to NRT on the far-right). This is not unexpected since many consumers believe that nicotine in cigarettes is the major cause of the smoking related diseases (Haddock et al. 2004; O’Connor et al. 2005a; Peiper et al. 2010). Furthermore, the participants perceived the addiction risks of VLN[®] with claims to be between e-cigarettes and NRT. This is also not unexpected since the participants seemed to understand from the claims, that VLN[®] had less nicotine and therefore should be less addictive. The study showed that non-smokers (subjects of legal smoking age, respective of the participant’s US state of residence, to 25-year olds subgroup – used as a proxy for youth smokers who may not be interviewed by law without parental consent) and former smokers were not interested in the product. The only group that showed any real interest in the product concept was smokers with an intention to quit. They responded as somewhat likely to use the product as compared to an indication of between somewhat likely and somewhat unlikely to use in smokers with no intention to quit. This is important because it shows that the participants understood the product claim labeling and could identify that this was a product for them.

The study design also included a VLN[®] pack without any claims. (b) (4)
the images of the VLN[®] control pack were (b) (4) presented to the subjects (b) (4)
this does not affect the overall interpretation of the study for the purposes of this MRTPA because the goal of this cell was to determine the impact of the design of the package

and trade dress on consumer behavior. Labeling without claims is not the subject or purpose of the Company's MRTPA.

As stated above, the goal of the study was to determine the impact of the potential claim labeling of VLN[®], i.e., to "provide data regarding how consumers perceive the risks to health from using the product, and the likelihood of trying the product." This was accomplished (b) (4) because the Marlboro Gold cell is the valid control cell in this analysis. The conclusions about VLN[®] with the claims "95% Less Nicotine" and "Helps reduce your nicotine consumption" are (b) (4) valid based on the relevant data sets, i.e., VLN[®] with claims vs. Marlboro representing the conventional cigarette, that were tested. We believe the (b) (4) VLN Control Cell is an unnecessary component of the study for the purposes of this MRTPA. (b) (4)

Finally, the FDA notes the spreadsheet file, MARC_QN_Appx_J_RawData_5180080_2018_Data_Excel_2Tabs.xlsx, submitted with XXII's May 17, 2019 MRTPA, has data in columns labeled "responseid" and "respid" that correspond for the first 254 respondents, but not for the remaining rows. MARC states that this is not an error. Both numbers are assigned by .NET, the underlying code of Conformat, the programming platform. The numbers are assigned as different points in time, along the survey process. There are various participants taking the survey at any one time and working through the survey at different paces and with different results; for example, completing or not completing the survey. MARC confirms that the columns or rows have not been missorted and the data as shown in the Excel file is in the proper order.