# Section III Executive Summary

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Section III. Executive Summary

The nicotine level in 22nd Century’s proprietary very low nicotine content (VLNC) cigarettes is at least 95% less as compared to all other cigarettes in the U.S. marketplace. The Company has developed VLN™ tobacco and VLN™ cigarettes for the express purpose of reducing cigarette smokers’ exposure to nicotine. More than 50 independent clinical studies have been conducted with the Company’s VLNC cigarettes; these studies conclusively demonstrate that use of VLNC cigarettes results in decreased cigarette consumption, reduction in nicotine absorption, reduction in other biomarkers of exposure, more quit attempts, and abstinence. While the Company is encouraged by these results, 22nd Century intends to make no reduced risk or cessation claims, direct or implied, for VLN™ cigarettes or VLN™ tobacco at this time. That 22nd Century includes information on cessation, dependence, and abstinence and references such terms in this submission should not be interpreted to mean that the Company intends to make any drug claims. The Company is requesting only Exposure Modification Orders at this time since
it believes that scientific evidence is not currently available to assess the long-term risks of the products without conducting long-term epidemiological studies.

A. Background

In 1994, Drs. Benowitz and Henningfield proposed gradually reducing nicotine levels of all cigarettes over a 10-15 year period. (Benowitz and Henningfield 1994). At the time, this created a firestorm in the public health community. There was much debate over the concept of a very low nicotine content cigarette and more debate over the merits of a gradual versus an immediate approach to reducing the nicotine level in cigarettes. Since then, numerous studies, including an 804-patient study by Donny (Donny et al 2015), have found substantial public health benefits associated with very low nicotine content cigarettes. And, in a recent landmark study by Dr. Hatsukami (Hatsukami et al 2018) of 1250 subjects over 20-weeks, it was demonstrated that in contrast to a gradual reduction of nicotine, an “immediate reduction of nicotine was associated with lower toxicant exposure across time, smoking fewer cigarettes per day, greater reduction in dependence, and more cigarette free days.” Now, after more than 20 years of public health research and hundreds of publications on the concept, 22nd Century is herein applying for FDA authorization to make an exposure modification claim for products that have the potential to change the historical course of public health and to help defeat the global tobacco epidemic.

It is well known that nicotine is the addictive agent in tobacco. In a June 16, 2010 press release, Dr. David Kessler, former FDA Commissioner, recommended, “The FDA should quickly move to reduce nicotine levels in cigarettes to non-addictive levels. If we reduce the level of the stimulus, we reduce the craving. It is the ultimate harm reduction strategy.” Shortly thereafter in a Washington Post newspaper article, Dr. Kessler said that the amount of nicotine in a cigarette
should drop from about 10 milligrams to less than 1 milligram. The products that are the subject of this MRTPA contain approximately 0.3 milligrams of nicotine per cigarette. More recently, Dr. Scott Gottlieb, the current FDA Commissioner, stated in a public FDA announcement on July 28, 2017:

The overwhelming amount of death and disease attributable to tobacco is caused by addiction to cigarettes – the only legal consumer product that, when used as intended, will kill half of all long-term users. Unless we change course, 5.6 million young people alive today will die prematurely later in life from tobacco use. Envisioning a world where cigarettes would no longer create or sustain addiction, and where adults who still need or want nicotine could get it from alternative and less harmful sources, needs to be the cornerstone of our efforts – and we believe it’s vital that we pursue this common ground. …. Looking at ways to reduce nicotine levels in cigarettes so that they are minimally or non-addictive …. is a cornerstone of our new and more comprehensive approach to effective tobacco regulation. ... The public health benefits at a population level kick in over time, as future generations of kids who may experiment with cigarettes find it far less likely to ever become addicted to nicotine, and to suffer the chronic diseases that they are at great risk of experiencing once addicted to combustible cigarettes.

Dr. Gottlieb’s public announcement revealed a comprehensive plan for tobacco and nicotine regulation. As part of such plan, on March 16, 2018, FDA published an advance notice of proposed rulemaking (ANPRM) announcing an intention to issue a proposed rule that, when finalized and effective, would limit the amount of nicotine in all cigarettes sold in the United
States (and perhaps in other combusted tobacco products) so that they are minimally addictive or non-addictive. In a coordinated press release, the FDA said that it believed “the public health benefits and the potential to save millions of lives, both in the near and long term, support this effort [to dramatically limit the amount of nicotine in all cigarettes sold in the United States].”

The ANPRM states:

Greatly reducing or eliminating the addictiveness of cigarettes would have significant benefits for youth, young adults, and adults. More than half of adult cigarette smokers make a serious quit attempt each year (quit for at least a day), many of whom do not succeed due to the addictive nature of these products. The establishment of a maximum nicotine level in cigarettes not only could increase the likelihood of successful quit attempts, but it also could help prevent experimenters (mainly youth and young adults) from initiating regular cigarette smoking. Therefore, rendering cigarettes minimally addictive or nonaddictive (however that were achieved) could help current users quit and prevent future users from becoming addicted and escalating to regular use. ... FDA hypothesizes that making cigarettes minimally addictive or nonaddictive, ... would significantly reduce the morbidity and mortality caused by smoking. ...if cigarettes were minimally addictive or nonaddictive, it is expected that many fewer youth and young adults would be subjected to the impacts of nicotine ... from cigarettes, nor would they suffer from the health and mortality effects of cigarette use. ... FDA expects that making cigarettes minimally addictive or nonaddictive (however that were achieved) may have significant benefits for youth by reducing the risk that
youth experimenters progress to regular use of cigarettes as a result of nicotine dependence. ... Similarly, limiting the nicotine in cigarettes could have significant benefits for adult tobacco product users, a large majority of whom want to quit but are unsuccessful because of the highly addicted nature of the products. ... Although many factors contribute to an individual’s initial experimentation with tobacco products, the addictive nature of tobacco is the major reason people progress to regular use, and it is the presence of nicotine that causes youth, young adults, and adult users to become addicted to, and sustain tobacco use.

When the FDA were to move forward in the product standard process and proceed to the next step of issuing a proposed rule, section 907(b)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387g(b)(1)) would require that FDA consider information submitted in connection with that proposed product standard regarding technical achievability of compliance. By way of this application, 22nd Century is demonstrating the technical achievability of the FDA’s proposed plan and seeks to offer, for the first time, a product that will meet the FDA’s stated objectives for such a product standard: “(1) Give addicted users of cigarettes the choice and ability to quit more easily by reducing the nicotine to a minimally addictive or nonaddictive level and (2) reduce the risk of progression to regular use and nicotine dependence for persons who experiment with the tobacco products covered by the standard.”

The core of 22nd Century’s VLN™ cigarettes is the Company’s VLN™ tobacco. This tobacco, produced using 22nd Century’s proprietary technology, grows with very low levels of nicotine. As nicotine production in tobacco is controlled by multiple genes in the plant, 22nd Century’s technology involves blocking or down regulating several genes in the tobacco plant and
then selecting for tobacco plant lines that produce the lowest levels of nicotine. VLN™ cigarettes are made with the Company’s proprietary VLN™ tobacco at a target specification level of 0.5 mg nicotine per gram of tobacco (dry weight).

22nd Century’s VLN™ tobacco was developed in 1998 and has since been used in many cigarettes under different names, including X-22, Xodus, Magic, MAGIC 0, MAGIC 2, Quest®, SPECTRUM®, PARE®, and VLN™. Figure III.A-1 Timeline of Various VLN™ Tobacco Products shows the timeline of the various cigarettes that have used VLN™ tobacco. Quest® cigarettes were developed and marketed by Vector Tobacco, Inc. under license from 22nd Century from 2002 to 2009. The family of Quest products included Quest 1 (a cigarette made of conventional tobacco), Quest 2 (a cigarette containing a blend of conventional tobacco and VLN™ tobacco), and Quest 3 (a cigarette made exclusively with VLN™ tobacco). Quest cigarettes were marketed to promote smoking cessation. In 2006, Vector filed an IND (69,185) with the FDA regarding the Quest products with VLN™ tobacco contained therein. 22nd Century has the legal right to use the information in the Vector IND and a copy of such IND is included in this MRTPA.
22nd Century developed X-22\(^1\) cigarettes with the intent of obtaining a drug claim for smoking cessation. The Company conducted a clinical study with X-22 under IND 103,589. Participants assigned to X-22 reduced their cigarette consumption, but there was no difference between X-22 and the active control in abstinence rates three months after the quit date. Currently, the development of X-22 is paused. A copy of the IND is included in this MRTPA.

Though no longer actively marketed, the cigarette brands Xodus, Magic, MAGIC 0, and MAGIC 2 also contained VLN™ tobacco. The Company is continuing development of these and other very low nicotine content (VLNC) cigarettes for international markets.

\(^1\) X-22 cigarettes are similar to VLN™ cigarettes. These two products essentially have the same design parameters and were made with the same materials and the same VLN™ tobacco. Both products have a target tobacco nicotine content of 0.5 mg/g. The difference between the two products is that X-22 used blend C-22 VLN and VLN™ uses blend.
In 2011, 22nd Century developed the SPECTRUM® line of research cigarettes in collaboration with independent researchers and officials from the National Institute on Drug Abuse (NIDA), the FDA, the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC). The main 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 nicotine contents and yields. SPECTRUM® products are available in 24 styles, in both regular and menthol versions, with 8 levels of nicotine in their tobacco. The amount of nicotine in the various styles of SPECTRUM® cigarettes is controlled by blending conventional nicotine content tobacco and VLN™ tobacco. The lowest nicotine level SPECTRUM® cigarettes contain only VLN™ tobacco.

PARE® cigarettes were developed by 22nd Century for potential marketing in the U.S. pursuant to a premarket authorization. These products are exactly the same as the very low nicotine versions of SPECTRUM® cigarettes (NRC102 and 103). 22nd Century submitted a PMTA/MRTPA for PARE® cigarettes in 2015. After receiving constructive feedback from the FDA on the application for PARE®, 22nd Century withdrew the PMTA/MRTPA for PARE® in 2017.

Based on such feedback from the FDA, and with the benefit of additional, extensive Company and independent research, 22nd Century is now submitting this MRTPA requesting orders under Section 911(g)(2) of the FD&C Act for claims regarding reduced exposure to nicotine (Exposure Modification Orders) for two VLN™ cigarette products: VLN™ King and VLN™ Menthol King. The Company has previously submitted a PMTA for the same products. Because it is critical for consumers to understand the basic nature of the products through disclosure of their very

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2 The SPECTRUM® product range has 8 different nicotine levels. Nicotine Research Cigarette (NRC)102 and 103 are the regular and menthol versions of SPECTRUM® containing a target nicotine level of 0.5 mg/ g tobacco (dry weight).
low nicotine content, the Company does not intend to make VLN™ cigarettes available to consumers in the United States in the absence of an MRTP order.

The Company has developed VLN™ tobacco and VLN™ cigarettes for the purpose of reducing cigarette smokers’ exposure to nicotine. The Company is requesting only Exposure Modification Orders at this time since it believes that scientific evidence is not currently available to assess the long-term risks of the products without conducting long-term epidemiological studies. The Company believes VLN™ cigarettes have the same risks as conventional cigarettes and the benefit of using the products comes from reducing nicotine exposure. The MRTPA requests FDA authorizations for the following three claims:

- Claim #1 under §911(g)(2): “95% less nicotine”
- Claim #2 under §911(g)(2): “Helps reduce your nicotine consumption”
- Claim #3 under §911(g)(2): “... greatly reduces your nicotine consumption”

Both of the VLN™ products (King and Menthol King) will carry the primary claim of “95% Less Nicotine” on the front and back of the pack. “Helps reduce your nicotine consumption” will appear on the front of the pack under the “95% Less Nicotine” statement. A similar claim on the back of the pack would state:

VLN™ smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption.
B. Product Description

22nd Century developed the VLN™ cigarettes that are the subjects of this application. The VLN™ cigarettes (Menthol King and King (non-menthol) cigarettes) are also exactly the same as the NRC102 and NRC103 SPECTRUM® very low nicotine research cigarettes. They are also exactly the same as the PARE® cigarettes that were the subject of the previous applications referenced above. The only difference between each respective regular or menthol VLN™, PARE® and SPECTRUM® NRC102/NRC103 brand style is the name of the product³. Studies have been conducted on VLN™ and SPECTRUM® cigarettes measuring smoke chemistry, abuse liability, smoking behavior, and topography. The results of the studies with VLN™ cigarettes are consistent with those published for SPECTRUM® NRC102/NRC103 cigarettes.

22nd Century produces VLN™ cigarettes in the same manner as conventional cigarettes, using materials, ingredients, and processes well-established in the cigarette industry. The product is designed to appear just like a conventional cigarette (Figure III.B-1. Diagram of VLN™ Cigarette.).

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³ SPECTRUM is made with the same base tipping paper as VLN™ but the paper is printed with a silver line and the word “SPECTRUM”.
The only difference between VLN™ and conventional cigarettes is that VLN™ cigarettes contain VLN™ tobacco. The Animal and Plant Health Inspection Service (APHIS) has concluded that the VLN™ tobacco (specifically variety Vector 42-21) and any progeny derived from hybrid crosses with other non-transformed tobacco varieties is safe to grow as tobacco and is not subject to regulation under 7 CFR part 340. Thus, use of VLN™ tobacco should have no environmental impact at the grower level. Since VLN™ cigarettes use the same materials, ingredients, and process as other conventional cigarettes and since VLN™ cigarettes are intended to replace conventional cigarettes, there should be no increased environmental impact from approval of this MRTPA for VLN™ cigarettes. It should be noted that VLN™ cigarettes are currently being produced under the SPECTRUM® brand name in 22nd Century’s manufacturing facility. There will be no changes in the manufacturing facility or waste stream as a result of the production of VLN™ cigarettes. If cigarette consumption declines as a result of the use of VLN™ cigarettes, there will be a reduction in the overall impact of conventional cigarettes on the environment.

VLN™ cigarettes are used like conventional cigarettes; there are no unique instructions for use of VLN™ cigarettes. VLN™ cigarettes are stable at room temperature for at least one year.
VLN™ cigarettes will be sold in traditional cigarette packaging, as seen below (Figure III.B-2. 3-D Image of Representative VLN™ Pack).
C. Summary of Analytical Studies and Quantitative Risk Assessments

VLN™ cigarettes are substantially lower in nicotine than any other cigarettes currently sold to consumers in the United States—whether measured on a cigarette, tobacco dry weight, or cigarette smoke yield basis. VLN™ cigarettes contain a target level of 0.5 mg of nicotine per gram of tobacco (dry weight). A survey of the top 100 leading cigarette brands in the U.S. showed that, on average, these cigarettes contained 19.4 mg of nicotine per gram of tobacco on a dry weight basis (nicotine content range = 14.7 to 33.2 mg/g). Accordingly, the nicotine content of VLN™ cigarette tobacco is 97% lower than the average nicotine content of the tobacco filler in the top 100 leading brands. When compared to the lowest nicotine content product of any of the top 100 leading US brands, “L&M 100,” the nicotine content of VLN™ is 96% lower. When compared
on a cigarette basis, the top 100 brands average 12.0 mg of nicotine and VLN™ averages 0.27 mg. Therefore, without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 brands in the U.S. Similarly, the amount of nicotine in smoke (yield) for VLN™ cigarettes is 0.03 mg/cig, which is also substantially lower than the top 100 cigarette brands’ nicotine smoke yields. The average nicotine yield for the top 100 brands was 0.903 mg/cig under ISO conditions (range 0.4 to 1.8). The average nicotine yield of VLN™ was 0.03 mg/cig, which represents a 97% reduction. Figure III.C-1. VLN™ nicotine content in tobacco and yield in smoke compared to the top 100 brands. below shows the relative relationships of filler nicotine content in the tobacco and smoke yield of VLN™ compared to the top 100 cigarette brands in the U.S. Figure III.C-2. VLN™ nicotine content in cigarettes compared to the top 100 brands.) shows the nicotine content in the top 100 brands on a cigarette basis. Because of the unique technology used to reduce nicotine and the absence of the technology in any other cigarette on the market, the Company firmly believes that the nicotine level in VLN™ is reduced at least 95% when compared to all other cigarettes in the marketplace and a comparator statement such as “leading brands”, “usual brand”, “typical brands”, or “top three brands” is not required.
Figure III.C-1. VLN™ nicotine content in tobacco and yield in smoke compared to the top 100 brands.
Figure III.C.2. VLN™ nicotine content in cigarettes compared to the top 100 brands.
VLN™ cigarettes are not considered to be less hazardous than conventional cigarettes. The Company compared the smoke chemistry of VLN™ cigarettes, under ISO conditions, with the smoke chemistry of the market-leading brands. The Harmful and Potentially Harmful Constituents (HPHCs) in the smoke of VLN™ cigarettes were similar to those measured in the smoke of the market-leading brands, with the exception of reductions in nicotine, acrolein, formaldehyde, benzo[a]pyrene, NNN, and NNK in the VLN™ cigarettes. The technology that makes VLN™ tobacco results in a reduction in the production of nicotine, NNN, and NNK by the plant. Essentially, the nicotine and TSNA production pathways in VLN™ tobacco plants are intentionally inhibited. This results in a slight accumulation of nitrogen in the plant. It is hypothesized that the plant continues to assimilate nitrogen with limited alkaloids as receivers for the nitrogen. This results in an increase in smoke ammonia as well as other nitrogen containing constituents, including 1-aminonaphthalene and 2-aminonaphthalene. Figure III.C-3. Comparison of HPHC’s of VLN™ to Market Leading Brands) graphically presents the HPHC levels from the market-leading brands compared to VLN™ and clearly shows meaningful reductions in VLN™ HPHCs.
A quantitative risk assessment was conducted on VLN™ and the market-leading cigarette brands to determine if the changes in HPHCs are likely to increase the risks of VLN™. These studies show that VLN™ had a distinctly lower estimated cancer and non-cancer risk profile when compared to the market-leading cigarette brands (Figure III.C-4. Cancer and Non-cancer Risks of VLN™ Compared to Market Leading Brands). The Company does not believe that these results
demonstrate that the product has reduced risks. The Company does believe that these results demonstrate that it is unlikely that VLN™ presents an increased risk to the consumer.

Figure III.C-4. Cancer and Non-cancer Risks of VLN™ Compared to Market Leading Brands

D. Summary of Other Nonclinical Studies

Based on the above data and the fact that the primary substantive difference between VLN™ cigarettes and conventional cigarettes is that VLN™ cigarettes contain considerably less nicotine, 22nd Century believes that VLN™ cigarettes are no more hazardous than conventional cigarettes. The Company, therefore, will make no claims of safety or reduced risk over conventional cigarettes.

Nonclinical studies with VLNC products, other than the constituent testing and quantitative risk assessment described above, are limited. Most nonclinical studies were
conducted with Quest 3⁴, a VLNC cigarette similar to but not the same as VLN™. These studies on Quest 3 were generally limited to special studies related to the effects of nicotine where testing used reduced nicotine cigarettes as one of the controls/treatments. As expected, the studies did not demonstrate any unique toxicities, except effects related to decreased nicotine.

E. Summary of Clinical Studies

The Company and independent researchers have conducted a substantial number of clinical studies using VLNC cigarettes, including SPECTRUM® cigarettes identical to the VLN™ products covered by this application. The studies indicate that VLNC cigarettes can help many cigarette consumers substantially reduce their nicotine and cigarette consumption, therefore bringing broad-based benefits to public health.

The lower level of nicotine in VLN™ cigarettes substantially reduces the level of nicotine in the blood when compared to other nicotine-delivery products. An abuse liability study with VLN™ King cigarettes demonstrated that the plasma nicotine levels were significantly reduced from those associated with usual brands and even less than 4 mg nicotine gum (Figure III.E-1. Plasma Nicotine Levels after ad libitum VLN™, Usual Brand and 4 mg Nicotine Gum (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum)). This is not unexpected since VLN™ cigarettes only contain a target level of 0.5 mg of nicotine per gram of tobacco as compared to 4 mg from the nicotine gum⁵. The time to maximum concentration (t_{max}) was essentially the same for VLN™ and for usual brand (Table III.E-1. Summary of baseline-adjusted plasma nicotine pharmacokinetic values.). This is to be expected since the route of exposure was the same. The

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⁴ Quest 3 used VLN™ tobacco yielding low levels of nicotine, but the product’s design characteristics were different.
⁵ The smoke yield of VLN™ cigarettes is 0.03 mg of nicotine per cigarette.
$t_{\text{max}}$ for gum was slower and different than smoking. Similar results were obtained with VLN™ Menthol Kings.

Figure III.E-1. Plasma Nicotine Levels after ad libitum VLN™, Usual Brand and 4 mg Nicotine Gum (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

Table III.E-1. Summary of baseline-adjusted plasma nicotine pharmacokinetic values.

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition</th>
<th>AUC  (ng*min/ml)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$t_{\text{max}}$ (min)</th>
<th>$T_{\frac{1}{2}}$ (min)</th>
<th>$K_{el}$ (1/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Brand</td>
<td>Controlled Use</td>
<td>770.80*</td>
<td>13.7#</td>
<td>8.29</td>
<td>123.49</td>
<td>0.0063</td>
</tr>
<tr>
<td>VLN™</td>
<td>Controlled Use</td>
<td>26.2*#</td>
<td>0.47*#</td>
<td>9.75</td>
<td>213.4</td>
<td>0.0098</td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>Controlled Use</td>
<td>342.77*</td>
<td>3.5*</td>
<td>33.6</td>
<td>125.36</td>
<td>0.0062</td>
</tr>
<tr>
<td>Usual Brand</td>
<td>Uncontrolled Use</td>
<td>879.75*</td>
<td>16.97*#</td>
<td>7.85</td>
<td>101.89</td>
<td>0.0078</td>
</tr>
<tr>
<td>VLN™</td>
<td>Uncontrolled Use</td>
<td>28.3*#</td>
<td>0.57*#</td>
<td>9.38</td>
<td>110.8</td>
<td>0.0123</td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>Uncontrolled Use</td>
<td>277.3*</td>
<td>3.2*</td>
<td>28.7</td>
<td>166.42</td>
<td>0.0078</td>
</tr>
</tbody>
</table>

* p<0.05 to Usual Brand  
# p<0.05 to Nicotine Gum
Primary studies with SPECTRUM® and VLN™ cigarettes and secondary supporting clinical studies with Quest, X-22, and Xodus cigarettes indicate that the cigarettes are well tolerated by users, but not as desirable to users as their usual brands. The VLN™ products do not provide a nicotine “throat hit” or the nicotine “rush” to which smokers are accustomed. In the VLN™ King abuse liability study, subjects were asked if they would “use the product again” after a four-hour ad libitum use session. On a scale of 0 to 100, with 0 being “Definitely Would Not” and 100 being “Definitely Would,” usual brand rated 95, nicotine gum 59 and VLN™ 34. VLN™ Menthol Kings were rated slightly higher. In a direct effect questionnaire, VLN™ Kings were rated as less satisfying than the usual cigarette brand, but not different from nicotine gum (Figure III.E-2. Mean direct effect of product questionnaire responses following product administration (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).). Similar results were obtained with VLN™ Menthol Kings.
The abuse liability study also measured craving and urges over time after smoking a single cigarette. VLN™ Kings did not suppress craving and urges in abstinent smokers to the degree that the usual brands did, but there was no difference between nicotine gum and VLN™ (Figure III.E-3. Mean tobacco/nicotine withdrawal questionnaire responses following product administration (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum.). These effects on smoking urge, cravings and satisfaction are well documented in the literature. For smokers who desire a cigarette, VLN™ Kings and VLN™ Menthol Kings have shown the ability to suppress the urge to smoke, just not to the extent that consumers’ usual brands do.
Figure III.E-3. Mean tobacco/nicotine withdrawal questionnaire responses following product administration (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving

There have been no serious adverse events attributed to SPECTRUM® or VLN™ cigarettes.

More than 50 clinical studies have been conducted on VLNC cigarettes which conclusively demonstrate that continued use of VLN™ cigarettes results in decreased cigarette consumption,
reduction in nicotine absorption, and reduction in other biomarkers of exposure. These effects also extend to nondaily intermittent smokers.

Studies indicate that use of VLN™ cigarettes can lead to substantial reductions in smoking among many users. Reduction in cigarettes per day (CPD) is a common end-point in the clinical studies. In the longest (20-weeks) and largest (1,250 subjects with no intention to quit) study to date on SPECTRUM®/VLN™ cigarettes, Dr. Hatsukami, et.al., observed more than a 50% reduction in CPD (Figure III.E-4. **CPD (Subjects were immediately (Immediate group) switched to VLN™ or gradually migrated (Gradual Group) using SPECTRUM cigarettes)**) (From Hatsukami et al 2018). This result is representative of all of the published studies. The degree of reduction appears to be related to the duration of use of VLN™ cigarettes. The longer a user smokes VLN™ cigarettes, the less s/he tends to smoke. Figure III.E-5. **Summary of CPD (dotted line is linear trendline).** is a summary of CPD reduction observed in the published studies. As shown in Figure III.E-5, there is a range in response from none to minimal after a few days to more than 50% after 140 days.

*Figure III.E-4. CPD (Subjects were immediately (Immediate group) switched to VLN™ or gradually migrated (Gradual Group) using SPECTRUM cigarettes) (From Hatsukami et al 2018).*
“Compensation” (smoking a greater number of cigarettes or puffing “differently” to obtain the level of nicotine desired by the smoker) is not a significant factor with VLNC cigarettes. Published studies show there are minimal initial changes to topography and that within a few days the topography is the same as usual brand. One way of measuring compensation is to measure CO boost (increase in exhaled CO relative to control indicating increased smoking). Among the published studies evaluating use of SPECTRUM® cigarettes none has reported CO boost suggestive of compensatory smoking. Indeed, Dr. Hatsukami observed a gradual decrease in exhaled CO over the course of the 20-week study (Figure III.E-6. CO Levels (From Hatsukami et al 2018)).
The “gold standard” for measuring reduced nicotine exposure is the amount of total nicotine equivalents (TNE) in the urine. Dr. Hatsukami observed a 57% reduction in TNE (Figure III.E-7. *Total nicotine equivalents (TNE) after 20-weeks* (From Hatsukami et al 2018).) in her 20-week study with SPECTRUM®/VLN™ cigarettes. Ranges from other published studies have observed reductions in TNE as high as 95%. For constituents that are reduced in the VLN™ tobacco, such as NNK and acrolein, there are parallel reductions in the biomarkers of exposure (Figure III.E-8. *Urinary metabolites of NNK (NNAL) and acrolein (3-HPMA)* (From Hatsukami et al 2018).).
Studies indicate that initial use of the VLN™ cigarettes leads to some withdrawal symptoms, while continued use of VLN™ cigarettes reduces smoking dependence and the urge to smoke. Reduction in smoking urge and craving with SPECTRUM®/VLN™ cigarettes has been observed to
varying degrees in more than 30 clinical studies. The most common way to measure smoking urge is the Questionnaire on Smoking Urges (QSU). This is a series of 10 questions presented to participants about how they feel “right now.” The results of the survey questions are combined into two groups, Factor 1 which represents urge to smoke and Factor 2 which represents withdrawal. Dr. Hatsukami measured smoking urges over 20-weeks and observed a decline (Figure III.E-9. *QSU Factor 1 Results* (From Hatsukami et al 2018)).

Clinical studies with VLNC cigarettes used in conjunction with nicotine replacement therapy leads to more smoke free days, more quit attempts, and abstinence. While the Company is encouraged by these results, it intends to make no reduced risk or cessation claims for VLN™.

**F. Projected Effects on the Population as a Whole**

The effect of the VLN™ product on the population as a whole was modeled starting with product introduction in 2020 (Figure III.F-1. *Diagram of Population Model*). The target market
for VLN™ cigarettes is current smokers who wish to reduce their nicotine consumption. Possible consequences of switching to VLN™ cigarettes include reduced cigarette consumption and increased quitting, with corresponding gradual reductions in morbidity and mortality rates. Under a base-case scenario, 22nd Century's model 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 by the year 2100 (cumulative) (Figure III.F-2. Base-case scenario of avoided cigarette-attributable deaths and life-years gained). Younger adults will experience the greatest long-term benefits due to their longer opportunity to switch to VLN™ cigarettes and then away from cigarettes entirely. Under an optimistic scenario, there will be almost 1 million avoided smoking-attributable deaths and almost 19 million life years gained (Figure III.F-3. Optimistic Scenario of Avoided Cigarette-attributable Deaths).

Figure III.F-1. Diagram of Population Model

Diagram showing the flow of individuals through different stages: New Adult Population, Conventional Cig. (CC) Smokers, Former Smokers, Never-Smokers, Initial VLN Smokers, Sustaining VLN Smokers, Deaths, with rates and proportions highlighted.
The FDA has announced an intention to issue a proposed rule that, when finalized and effective, would limit the amount of nicotine in cigarettes (and perhaps other combusted tobacco products) so that they are minimally addictive or non-addictive. A study by Dr. Ben Apelberg
(Apelberg, 2018), modeled the effect of a potential nicotine product standard. The model compared a baseline scenario (assuming that cigarette smoking will continue to decline based on recent trends in smoking initiation and cessation) with a policy scenario in which a product standard is put in place in 2020 to lower levels of nicotine in cigarettes and other combustible tobacco products that are highly likely to serve as substitutes for traditional cigarettes (i.e., roll-your-own tobacco, pipe tobacco, non-premium cigars). The model took into account the following potential behaviors: completely quitting cigarettes; switching from combustible to non-combustible tobacco products; using two or more tobacco products; becoming a new smoker; and becoming a new user of non-combustible products instead of becoming a smoker. Both scenarios are projected through the end of the century. According to this model, if the FDA’s nicotine reduction policy were put in place by 2020, approximately 5 million additional adult smokers would quit smoking within just one year of implementation, compared to the baseline scenario. In the years following, smoking rates would decline even more significantly. The study estimates that only about 1.4 percent of the U.S. adult population would smoke cigarettes by 2100, in part because more than 33 million people would avoid becoming regular smokers. A scenario was constructed using 22nd Century’s model assuming a mandated reduction in cigarette nicotine to minimally addictive levels in the year 2020, similar to Dr. Apelberg’s assumptions. In this scenario, 22nd Century’s model predicts about 8.2 million avoided smoking-attributable deaths and 150 million life-years gained by the year 2100, a result remarkably similar to Dr. Apelberg’s base-case (8.5 million and 134 million, respectively).
G. Effect of VLN™ and its Marketing on Tobacco Use Behavior

As part of the MRTPA development program, qualitative perception studies were conducted with reduced risk and reduced exposure statements. The statements were modified over the course of four different studies. The last study evaluated only reduced exposure statements. Evaluation of the final statements included on the packs indicated that consumers did not interpret the VLN™ packaging or the VLN™ exposure modification claims to indicate that the VLN™ cigarettes were significantly safer than conventional cigarettes. However, there was confusion by smokers about the role of nicotine in smoking-related disease. Accordingly, in developing the packaging for submission in the MRTPA, the Company added an additional statement to each pack to reinforce that VLN™ cigarettes are not safer than conventional cigarettes.

Nicotine is addictive. 
Less nicotine does NOT mean safer. All cigarettes can cause disease and death.

The proposed VLN™ products’ modified exposure claims did not interest non-smokers, former smokers, or youth. All rated the product concept as definitely would not purchase and definitely could not envision using the product (Figure III.G-1. Purchase and Use Intent for VLN™, VLN™ NC and Marlboro Gold)⁶.

⁶ VLN™ NC is a pack with no claim messages. The product was presented as a new conventional cigarette.
Consumers understood the health risks and risk of addiction of tobacco products in general. They placed VLN™ on a continuum of risk next to conventional cigarettes (Figure III.G-2. *Perceived Health Risks of VLN™ and Nicotine Containing Products*).
Exposure to the VLN concept did not change the consumers perception of the risks of the other tobacco products. Only current cigarette smokers expressed any meaningful interest in trying, using, or purchasing VLN™ cigarettes. The interest and intent were higher than Marlboro Gold, the Number 1 selling cigarette in the United States. Current smokers perceived the risk of addiction of VLN to be between e-cigarettes and NRT, that is, they understood that VLN™ had less nicotine and could be potentially less addicting (Figure III.G-3. Perceived Addiction Risks of VLN™ and Nicotine Containing Product). Smokers with an intent to quit had a higher perception of the health risks and risk of addiction of tobacco products and VLN™ than smokers with no intent to quit.

Figure III.G-3. Perceived Addiction Risks of VLN™ and Nicotine Containing Product
The overall results of the study showed that participants understood the modified exposure message and perceived that VLN™ poses some health and addiction risks. Furthermore, the results demonstrate that the VLN™ modified exposure message did not mislead participants into believing that VLN™ is less harmful or that VLN™ poses less health risk as compared to other tobacco products.

H. Addiction and Cessation

Nicotine is the substance primarily responsible for causing addiction to tobacco products. VLN™ cigarettes have substantially less nicotine than conventional cigarettes. Nonetheless, the Company does not intend to make any claims, direct or implied, that VLN™ cigarettes diagnose, cure, mitigate, treat, or prevent tobacco or nicotine addiction. That 22nd Century includes information on cessation, dependence, and abstinence and references such terms in this submission should not be interpreted to mean that the Company intends to make any drug claims.

I. Cited Literature

22nd Century Group, 2011. “A Prospective, Double-Blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of X-22 as a Smoking Cessation Aid (IND 103,589).”


Vector Tobacco Inc. 2006. “A Prospective, Double-Blind, Randomized, Active Controlled, Parallel Group, Multicenter Phase II Clinical Trial to Evaluate the Effectiveness of Quest Alone or in Combination with Nicotine Replacement Therapy as a Smoking Cessation Aid. (IND 69,185).”