July 16, 2018

SUBMITTED VIA WWW.REGULATIONS.GOV

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-N-6189, Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

Dear Madam or Sir:

22nd Century Group, Inc. ("22nd Century" or the "Company") hereby submits this public comment on the Advance Notice of Proposed Rulemaking, Tobacco Product Standard for Nicotine Level of Combusted Cigarettes ("ANPRM") by the U.S. Food & Drug Administration ("FDA").

Every day, thousands of young people smoke their first cigarettes. For many, this leads to a lifetime of addiction and many serious health consequences. While nearly 7 in 10 smokers wish to stop smoking, the majority are unable to do so. In 2018, it is estimated that nearly 38 million adults in the United States smoke cigarettes and more than 16 million people live with a smoking related disease.¹
While cigarettes are already subject to marketing restrictions, excise taxes and warning labels, more must be done.

22nd Century believes that Very Low Nicotine Content ("VLNC") cigarettes containing only minimally or non-addictive levels of nicotine will enable tens of millions of people to either stop smoking or to never develop the addiction to smoking. Independent clinical trials have shown that 22nd Century’s proprietary VLNC cigarettes enable smokers to disassociate the act of smoking from the rapid intake of nicotine. Accordingly, smoking consumption is reduced, withdrawal symptoms are lessened, and many more smokers attempt to quit. VLNC cigarettes are so promising, research published in the May 2018 edition of The New England Journal of Medicine estimates that in the first year after implementation of the FDA’s plan to limit cigarettes to minimally or non-addictive levels of nicotine, approximately 5 million people would stop smoking and, in as few as five years after implementation of the FDA’s plan, more than 13 million people would stop smoking.

Supplying the U.S. tobacco industry with tobacco containing very low levels of nicotine is eminently feasible. Since tobacco plants produce a prodigious number of seeds, 22nd Century can produce sufficient quantities of the Company’s proprietary VLN™ tobacco seed for the entire U.S. market in just one growing season. 22nd Century is willing to license the use of the Company’s VLN™ tobacco and technology to ALL interested companies. Therefore, every company will be able to comply with the new FDA rule to require that all cigarettes sold in the United States contain only minimally or non-addictive levels of nicotine. The opportunity to license the use of 22nd Century’s VLN™ tobacco and technologies eliminates any
argument by tobacco companies that contend it is not feasible or achievable to comply with the new FDA nicotine reduction rule. As described in greater detail herein, the case for enacting a national nicotine policy as envisioned by the FDA is compelling, feasible, and vitally urgent for the protection of public health.

In this public comment, 22nd Century will: (1) provide a background introduction to 22nd Century and the Company’s proprietary VLN\textsuperscript{TM} tobacco technology, (2) provide specific information in response to the ANPRM request for comments, (3) discuss the peer-reviewed and published, independent clinical studies conducted with 22nd Century’s VLNC cigarette, (4) discuss the planned timing of the Company’s submission of its Modified Risk Tobacco Product (“MRTP”) application to the FDA for VLNC cigarettes, and (5) advocate for the prompt implementation of the FDA’s nicotine reduction rule for the protection of public health.

1. **Background Introduction of 22nd Century**

22nd Century is a publicly-traded company on the New York Stock Exchange American Market ("NYSE American") under the trading symbol "XXII." All the information contained in this public comment by 22nd Century is publicly available information.

22nd Century is a plant biotechnology company with an important mission: To Reduce the Harm Caused by Smoking. The Company’s genetic engineering technology and plant breeding expertise allows it to regulate the level of nicotine (and other nicotinic alkaloids) in the tobacco plant. Because of this unique technology, 22nd Century is able to grow tobacco with significantly less nicotine than tobacco used in conventional cigarettes.
In 2010, the National Institute on Drug Abuse ("NIDA"), which is part of the National Institutes of Health ("NIH"), contacted 22nd Century to develop and produce research cigarettes with various levels of nicotine (from very low levels to conventional levels of nicotine). 22nd Century met with officials from NIDA, the FDA, RTI International ("RTI"), the Centers for Disease Control and Prevention ("CDC"), and the National Cancer Institute ("NCI") to design these research cigarettes. 22nd Century subsequently agreed, under a subcontract with RTI, to produce and supply variable nicotine content research cigarettes for NIDA, which have been subsequently distributed by RTI for NIDA to independent researchers for clinical studies. These proprietary research cigarettes were, and continue to be, produced under 22nd Century's mark: SPECTRUM®. The SPECTRUM® research cigarette contract was renewed with 22nd Century in 2015 for an additional five years.

Since 2011, well respected and experienced scientists have used 22nd Century's SPECTRUM® research cigarettes to conduct many important independent clinical trials. To date, 22nd Century has provided more than 24 million SPECTRUM® research cigarettes for use in independent clinical studies. A list of completed clinical studies using cigarettes made with 22nd Century’s VLN™ tobacco is included with this submission. A list of ongoing clinical studies using 22nd Century’s SPECTRUM® research cigarettes is also included with this submission.

While the FDA carries out the rule-making process to require that all cigarettes sold in the United States contain only minimally or non-addictive levels of nicotine, 22nd Century is preparing to submit an MRTP application to the FDA to obtain a reduced exposure marketing
authorization for the Company’s VLNC cigarettes. Since VLNC cigarettes made with 22nd Century’s proprietary VLN™ tobacco are the subject of numerous completed and on-going independent clinical studies, 22nd Century believes that there are sufficient scientific results to support the Company’s MRTP application.

2. **Specific information in response to ANPRM request for comments**

   **A. SCOPE**

   22nd Century has no position on the scope of the FDA’s reduced nicotine standard. 22nd Century desires to inform the FDA that the Company’s technology development on VLN™ tobacco is currently applicable to traditional cigarette tobaccos, including burley, Oriental, and flue-cured varieties. However, the Company’s technology also could be made applicable to other tobaccos.

   **B. MAXIMUM NICOTINE LEVEL**

   Based on the Company’s VLN™ tobacco growing experience, 22nd Century submits that the FDA’s reduced nicotine standard should be set at a target nicotine content level of 0.5 mg nicotine per gram of tobacco (dry weight) as measured in the tobacco filler itself. By definition, tobacco is an agricultural crop. Tobacco characteristics cannot be controlled to the same level of precision that is achievable in drugs or medical devices. Variations will occur based on growing conditions, location, and curing conditions. Therefore, the nicotine standard set by FDA should also allow for some variation. A nicotine target of 0.5 +/- 0.2 mg per gram of tobacco (dry weight) falls well within the range suggested by well-known scientists, including Dr. Eric Donny
(≤0.4 mg/g)^2, Dr. Dorothy Hatsukami (0.4 to 0.5 mg nicotine per gram of tobacco)^3 and Dr. Neil Benowitz (0.6 mg per cigarette).^4 Based on the fact that cigarettes contain only 0.7 grams of tobacco, 22nd Century's proposed maximum level of nicotine content of 0.7 mg/gm (0.5 +/- 0.2) tobacco would result in a cigarette containing 0.49 mg nicotine per cigarette. In 2015, The New England Journal of Medicine published “Reducing the Nicotine Content to Make Cigarettes Less Addictive.” Donny et al., concluded that data from the study suggests, as compared with cigarettes of conventional nicotine content, low nicotine cigarettes were “associated with reductions in smoking, nicotine exposure, and nicotine dependence, with minimal evidence of nicotine withdrawal, compensatory smoking, or serious adverse events.” Therefore, a nicotine content range of 0.5 +/- 0.2 mg/g is achievable and does not impact the “non-addictive or minimally addictive” properties of 22nd Century’s VLN™ tobacco.^5

1. Any VLNC Product Standard Must Be Based on The Nicotine Content of the Tobacco Leaf and not on the Nicotine Yield of the Smoke.

Both public health experts and courts have documented the history of deception by traditional cigarette manufacturers advertising their products as providing reduced exposure to tar and nicotine, thereby exploiting the tar and nicotine measurements by the Federal Trade Commission (“FTC”). Traditional cigarette manufacturers were fully aware that consumers could easily overcome design changes to filters or papers and/or increase their smoking to compensate for the purported reduced nicotine levels in such conventional cigarettes. The Family Smoking Prevention and Tobacco Control Act of 2009 (the “Tobacco Control Act”) itself recognizes the fallacy of achieving reduced nicotine exposure through design changes by
prohibiting the use of “light,” “low,” “mild,” or similar descriptors for cigarettes and other tobacco products absent FDA approval of an MRTP application. The only way to ensure that VLNC cigarettes do, in fact, provide consumers with minimally or non-addictive levels of nicotine is to go to the source – imposing a standard on the amount of nicotine contained in the tobacco itself.

2. The Agricultural Viability of Growing Tobacco Leaf that Meets a 0.5 mg/g Product Standard Is Well-Established.

The production history of VLN™ tobacco to date shows that tobacco with a nicotine content meeting a target of 0.5 +/- 0.2 mg/g (dry weight) can be grown and supplied dependably. In fact, 22nd Century has been developing, growing, and producing finished research cigarettes with very low nicotine tobacco for more than 8 years. In the year 2011, the Company’s X-22 product (a smoking cessation product; IND #103,589) was made from tobacco with a nicotine content of 0.51 mg/g (dry weight). The Company’s SPECTRUM® research cigarettes (produced under contract with RTI for NIDA) have been made on a continuous basis since 2011, with the nicotine content in the tobacco ranging from 0.37 to 0.62 mg/g (wet weight). These SPECTRUM® research cigarettes include regular and menthol versions. Similarly, 22nd Century’s prior MRTP application filed with the FDA in 2015, and the Company’s enhanced MRTP application to be filed with the FDA before the end of 2018, include regular and menthol cigarettes. Nicotine content varies from 0.45-0.57 mg/g (wet weight). The analyses on various versions of the Company’s products during development are shown below.
<table>
<thead>
<tr>
<th>Product</th>
<th>Year</th>
<th>Nicotine Concentration in Filler (mg/g tobacco (wet weight))</th>
<th>Nicotine Concentration in Filler (mg/g tobacco (dry weight))</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-22</td>
<td>2011</td>
<td>0.45</td>
<td>0.51</td>
</tr>
<tr>
<td>SPECTRUM® 01A</td>
<td>2011</td>
<td>0.41*</td>
<td>0.47*</td>
</tr>
<tr>
<td>SPECTRUM® 02A</td>
<td>2011</td>
<td>0.42*</td>
<td>0.48*</td>
</tr>
<tr>
<td>SPECTRUM® 03A</td>
<td>2011</td>
<td>0.37</td>
<td>0.42*</td>
</tr>
<tr>
<td>SPECTRUM® 04A</td>
<td>2011</td>
<td>0.39</td>
<td>0.44*</td>
</tr>
<tr>
<td>SPECTRUM® 05A</td>
<td>2011</td>
<td>0.44</td>
<td>0.50*</td>
</tr>
<tr>
<td>SPECTRUM® 06A</td>
<td>2011</td>
<td>0.41</td>
<td>0.47*</td>
</tr>
<tr>
<td>SPECTRUM® 04A</td>
<td>2015</td>
<td>0.62</td>
<td>0.70*</td>
</tr>
<tr>
<td>Pare Menthol</td>
<td>2015</td>
<td>0.55</td>
<td>0.62*</td>
</tr>
<tr>
<td>Pare Regular</td>
<td>2015</td>
<td>0.57</td>
<td>0.65*</td>
</tr>
<tr>
<td>Pare Menthol</td>
<td>2018</td>
<td>0.47</td>
<td>0.54</td>
</tr>
<tr>
<td>Pare Regular</td>
<td>2018</td>
<td>0.50</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*Nicotine dry weight was not measured. Nicotine dry weight content was estimated based on an assumed water content of 13.5%.

C. IMPLEMENTATION

Any nicotine standard requiring a minimally or non-addictive level of nicotine in cigarettes must be implemented in one step – all combustible cigarettes must be manufactured at that nicotine level immediately upon the effective date of the FDA rule. A staggered-step process allowing for the gradual reduction of nicotine will undermine the FDA's public health...
goals, create confusion in the marketplace, and disadvantage both growers and small manufacturers.

As the FDA has noted previously, a gradual step-down approach in nicotine has been demonstrated to result in partial “compensation” by smokers. The interim nicotine levels tested were such that the smokers could change their smoking behavior to intake more nicotine by smoking more frequently or inhaling more deeply.

In addition, a step-down approach would lead to confusion among smokers. Allowing cigarettes with different nicotine levels on the market at the same time would undermine the message to consumers that they need to break their addiction and would allow smokers to compensate by switching between cigarettes with different nicotine levels during the transition period. Manufacturers could encourage such compensation by marketing brand styles with different nicotine levels during each “step-down” period. A staggered approach to nicotine reduction could also lead to manufacturers manipulating the process by, for example, dumping higher nicotine products into the market just prior to the effective date of each “step down,” thereby slowing the process of moving existing smokers to VLNC cigarettes and stopping the initiation of smoking by underage youth and other non-smokers. In its public comment to the ANPRM as filed on July 12, 2018, the Center for Tobacco Research Control & Education at the University of California, San Francisco (“UCSF”) likewise stated, in support of an immediate approach to nicotine reduction, (i) its concerns about manufacturers manipulating the process in a staggered approach to nicotine reduction and (ii) the body of scientific evidence indicates that a rapid reduction of nicotine in cigarettes would be most beneficial to public health.
Last fall, at a conference in Vermont, Dr. Dorothy Hatsukami, a well-known and highly respected tobacco researcher, revealed the core results of a recently completed, but not yet published, 1,250-patient, 20-week study that compared smokers who were assigned to: (i) an immediate reduction to VLNC cigarettes; (ii) a gradual reduction in reduced nicotine content cigarettes; or (iii) normal nicotine content cigarettes. Dr. Hatsukami publicly disclosed at the Vermont conference that “an immediate approach [to nicotine reduction] is most likely to lead to less harm.” Further, Dr. Hatsukami pointed out that the study data indicates compensatory smoking is less likely to occur with an immediate reduction in nicotine, and that there was a “greater likelihood of more rapid smoking cessation” with the immediate approach to nicotine reduction. Dr. Hatsukami has also stated, in her publicly filed comments to the ANPRM, that the full results of the 1,250-patient clinical study are under peer review prior to being published in the near future.

Finally, both growers and small manufacturers would be hurt by a “step-down” approach to nicotine reduction. Requiring reductions in nicotine content in tobacco leaf on a staggered basis would force farmers to switch tobacco seeds and growing practices at each interim step. Smaller manufacturers would need to expend the financial and human resources required for transition to VLNC cigarettes multiple times instead of just once. There is no scientific, economic, or public health justification to support a step-down approach in nicotine reduction.
D. ANALYTICAL TESTING METHOD

As previously discussed, any reduced nicotine standard must be based on nicotine content in the tobacco, not on smoke constituent yields. Content-based standards will provide a more precise measure of the nicotine potentially available to the smoker. Content-based standards will also be immune to marketplace manipulation previously experienced during the marketing of so-called “light,” “low tar,” and “low nicotine” cigarettes based on “smoking machine” yields. The reduced nicotine standard should be based on dry weight measurements of nicotine content in the tobacco to correct for any differences in the amount of water in the tobacco.

In the year 2005, the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) first published its Recommended Method No. 62 – Determination of Nicotine in Tobacco and Tobacco Products by Gas Chromatographic Analysis. The CORESTA method has become an industry standard. Both in-house and third-party laboratories are experienced in testing under Recommended Method No. 62. Thus, there exists a documented, widely used, and validated method to measure nicotine content in tobacco. The CORESTA measurement method should be adopted as the method of choice by the FDA.

E. TECHNICAL ACHIEVABILITY

The FDA’s stated goal to render cigarettes minimally or non-addictive is readily and imminently achievable. 22nd Century already produces VLNC cigarettes that are described in independent scientific literature as “minimally” addictive. These VLNC cigarettes are available as a part of 22nd Century’s SPECTRUM® research cigarette line. The 22nd Century target
nicotine level for the very low nicotine SPECTRUM® brand is less than 0.7 mg per gram of dry tobacco filler. While Dr. Hatsukami and other independent researchers advocate for a nicotine content of 0.4 to 0.5 mg nicotine/g tobacco (wet weight) as the minimally or non-addictive levels for nicotine, 22nd Century believes that a nicotine content target of 0.5 mg/g (dry weight) with an acceptable variation of ± 0.2 mg/g is a better representation of the actual tobaccos grown, tested, and used in the clinical studies with the very low nicotine brands styles of the Company’s SPECTRUM® research cigarettes.

In preparation for a final FDA nicotine standard, 22nd Century has commenced growing increased amounts of the Company’s proprietary VLTM tobacco to support potential licensing transactions with third-party companies. In addition to the Company’s existing VLTM tobacco varieties, 22nd Century recently expanded the Company’s VLTM tobacco portfolio to include non-GMO flue-cured and non-GMO burley tobaccos. 22nd Century is also working on the development of VLTM Oriental tobacco varieties. 22nd Century understands that most tobacco brands use blends of different tobacco varieties to achieve their characteristic tastes. With VLTM flue-cured, VLTM burley, and soon Oriental VLTM tobacco varieties available, 22nd Century is well-prepared for the FDA’s new reduced nicotine standard. 22nd Century collectively refers to all the Company’s various types of very low nicotine tobacco under the trademark name: VLTM tobacco.

22nd Century has a portfolio of patented technologies that reduce nicotine in burley and flue-cured tobacco plants. The Company also continues to develop new VLTM tobacco varieties with improved agronomic traits. 22nd Century has proprietary rights and/or plant
variety protections for all of the Company's VLN™ tobacco varieties and technologies. 22nd Century is willing to license the use of the Company’s VLN™ tobaccos and technologies to all interested companies. The opportunity for companies to license and use 22nd Century’s unique VLN™ tobaccos and proprietary technologies negates any argument by third-party tobacco companies that contend it is not feasible or achievable for such tobacco companies to comply with the new FDA nicotine reduction rule.

The supply of VLN™ seed for VLN™ tobacco production is not a limiting step in adoption of the use of VLN™ tobacco to comply with the new FDA rule. For example, one tobacco plant yields more than 100,000 seeds; fewer than 25 acres of VLN™ tobacco plants will provide sufficient VLN™ seed to grow enough VLN™ tobacco to make 258 billion cigarettes—a 12-month supply for the entire U.S. cigarette market.

The VLN™ seed availability schedule for VLN™ tobaccos is summarized below:

- VLN™ burley Vector 21-41 seed is available now. 22nd Century can provide this seed to produce the entire quantity of tobacco consumed in the U.S. cigarette market.
- 22nd Century has exclusively licensed from North Carolina State University several flue-cured and burley tobacco plant lines that grow with very low nicotine levels. These new plants contain no foreign genetic material (non-GMO) and will compliment 22nd Century's existing very low nicotine plant portfolio.
- VLN™ non-GMO flue-cured tobacco is in the final stages of development by 22nd Century.
- VLN™ non-GMO burley tobacco is also in the final stages of development by 22nd Century.
- VLN™ Oriental tobacco is also under development by 22nd Century.

While 22nd Century understands that most existing tobacco brands use blends of different tobacco varieties to achieve their characteristic tastes, any changes in taste or sensory experience between highly addictive conventional tobacco and VLN™ tobacco should be secondary to the FDA’s development and implementation of a reduced nicotine standard. The FDA’s stated public health goal is to create a reduced nicotine standard that motivates current smokers to attempt to quit or to move down the “continuum of risk” to non-combustible products. VLNC cigarettes are not intended to be a permanent replacement for current combustible cigarettes. In fact, VLNC cigarettes do not contain enough nicotine for compensatory smoking. Instead, VLNC cigarettes are intended to give smokers a greater ability to break or change the source of their nicotine addiction in a relatively short period of time. Any change in “smoker acceptability” is not a critical element of the FDA reduced nicotine standard. However, independent clinical studies using 22nd Century’s SPECTRUM® research cigarettes measured smoker reaction to the taste of the product and determined VLNC content cigarettes to be acceptable.⁵
F. POSSIBLE COUNTERVAILING EFFECTS

Initial use of cigarettes containing VLN™ tobacco may result in smokers attempting to compensate for lower levels of nicotine.0,10 Clinical studies indicate that the smoking topography of SPECTRUM® cigarettes (after the first two weeks of use) is not different from the smoking topography of conventional cigarette brands. However, VLNC cigarette consumption and biomarkers of exposure are reduced after only six weeks of use.5,11 There may be a small incremental increase in exposure to tobacco smoke toxicants in the initial days of use; however, continued use during such 6-week period will result in overall reduced exposure.

G. OTHER CONSIDERATIONS

1. The FDA Must Implement a Quick, Efficient Process to Ensure that VLNC Cigarettes Are Promptly Made Available to Smokers.

In order for the FDA to achieve its public health goals, the FDA must adopt a marketing application process that allows for quick, efficient review of VLNC cigarettes while ensuring compliance with the reduced nicotine standard. The FDA has both the authority and the demonstrated ability to create a streamlined “substantial equivalence” (“SE”) process to ensure ready-to-market VLNC cigarettes are available to smokers without undue delay.

Manufacturers ready to market a VLNC cigarette should be able to file an abbreviated SE application focused on demonstrating to the FDA’s satisfaction that the product does in fact contain tobacco that meets the reduced nicotine requirements of the new FDA rule. Under its
current authority, the FDA can require manufacturers (and, if it so chooses, suppliers) to demonstrate that the product complies with the reduced nicotine product standard.

An abbreviated SE application for VLNC cigarettes should require specific data to show that the cigarettes meet the FDA’s reduced nicotine content standard, including the following:

- Disclosure of the tobacco blends of the current VLNC cigarette and its predicate;
- Disclosure of the strain/seed of VLNC tobacco used in the cigarette and its supplier;
- Disclosure of known nicotine reduction processes (if any) used to meet the reduced nicotine standard;
- Batch data (either internal or from certified third-party testing laboratories) showing that the finished product meets the reduced nicotine standard;
- Certification that the only change to the predicate product is changing of the tobacco blend to meet the reduced nicotine standard; and
- Any change to the design, other materials, or ingredients in the VLNC tobacco cigarette would require submission of a full SE application, including the information above.

The FDA also has the authority to ensure continued compliance with a reduced nicotine standard. Manufacturers can be required to submit, on a periodic basis, testing reports documenting that the manufacturer’s products continue to meet the target nicotine level set forth in the new FDA reduced nicotine standard.
3. **Peer-reviewed and published independent clinical studies**

The peer-reviewed and published results of the many independent clinical studies conducted with 22nd Century’s VLN™ tobacco provide a solid scientific foundation for the FDA’s proposed new rule to require that all cigarettes sold in the United States contain only “minimally or non-addictive” levels of nicotine. Dozens of studies have been conducted with Quest 3 cigarettes containing 22nd Century’s VLN™ tobacco, 22nd Century’s SPECTRUM® research cigarettes, and 22nd Century’s Xodus cigarettes. These studies demonstrate that:

- Smokers do not compensate when using cigarettes containing 22nd Century’s VLN™ tobacco.\(^5,11\)

- Smokers lower their cigarette consumption when using cigarettes containing 22nd Century’s VLN™ tobacco.\(^5,11\)

- Biomarkers of exposure are reduced because of the reduced nicotine intake and the reduced cigarette consumption when using cigarettes made with 22nd Century’s VLN™ tobacco.\(^5,11,12\)

- Cigarette dependence is reduced when using cigarettes containing 22nd Century’s VLN™ tobacco\(^5,11\)

- There is an increased number of quit attempts when using cigarettes containing 22nd Century’s VLN™ tobacco.\(^5\)
- Marijuana\textsuperscript{13} and alcohol\textsuperscript{14} consumption is not increased by the use of cigarettes containing 22nd Century’s VLNTM tobacco.

4. **22nd Century’s MRTP application**

As the FDA develops its reduced nicotine standard, 22nd Century is expanding the Company’s development of VLNTM tobaccos and tobacco products. 22nd Century recently initiated three clinical studies\textsuperscript{15,16,17} investigating the behavioral and biochemical responses to the Company’s proprietary VLNC tobacco cigarettes. Those studies, together with the numerous completed, independent clinical studies on 22nd Century’s VLNTM tobacco, will form the basis of 22nd Century’s resubmission to the FDA of an MRTP application before the end of 2018 for the Company’s VLNC tobacco cigarettes, which will contain a target nicotine content level of 0.5 +/- 0.2 mg/g (dry weight) of tobacco. This MRTP submission will include new studies on abuse liability, smoking behavior, and topography using 22nd Century’s VLNC menthol and non-menthol cigarettes. In addition, HPHC data comparing 22nd Century’s VLNC cigarettes to market leading conventional tobacco cigarette brands will be submitted. In this MRTP application, 22nd Century will seek FDA authorization to introduce VLNC cigarettes to the market with modified exposure statements disclosing the very low nicotine content of the product.
5. **22nd Century strongly advocates a prompt implementation of the FDA’s proposed nicotine reduction rule.**

Development by the FDA of a reduced nicotine standard for combustible cigarettes is one of the most important public health initiatives of this generation. The Tobacco Control Act grants the FDA authority over the regulation of all tobacco products in the United States. While the Tobacco Control Act prohibits the FDA from banning cigarettes outright, it allows the FDA to require the reduction of nicotine and other compounds in tobacco and cigarette smoke. Tobacco use remains the leading cause of preventable disease and death in the United States, causing more than 480,000 deaths per year and with direct health care and lost productivity costs totaling nearly $300 billion each year in the United States. The CDC states that in the year 2015, nearly 7 in 10 (68%) adult cigarette smokers wanted to stop smoking and more than 5 in 10 (55.4%) adult cigarette smokers had made a quit attempt in the prior year. The physical and financial destruction wrought by cigarettes is enormous and makes a compelling case for prompt changes to the nicotine content in cigarettes. **Indeed, smokers themselves overwhelmingly support a nicotine reduction mandate. In the year 2017, 22nd Century commissioned a survey by Harris Poll that found 68% of U.S. adults agree that the government should mandate that all cigarettes have very low, non-addictive levels of nicotine.**

On May 3, 2018, *The New England Journal of Medicine* published an FDA study that stated that (i) in the first year of implementation of the new FDA reduced nicotine rule more than 5 million people would stop smoking in the United States, (ii) in the first five years after the
implementation of the new FDA rule more than 13 million people would stop smoking in the United States, and (iii) by the end of this century more than 33 million Americans would either stop smoking or never develop the addiction to smoking. Every day that passes without implementation of a new FDA rule on reduced nicotine sees thousands of young people smoke their first cigarette and more than 2,000 youth and young adults, who have been occasional smokers, become daily smokers.\footnote{19}

In their May 21, 2018 public letter to FDA Commissioner Dr. Scott Gottlieb, the American Heart Association, the American Cancer Association, the American Medical Association and dozens of other public health and medical organizations described the “massive public health benefits” that will result from the adoption of the FDA’s vital plan to dramatically reduce nicotine in cigarettes: “Every day that passes means more kids moving from experimentation to addiction and more adults who want to quit and try to quit, but remain addicted to a lethal product. We urge the FDA to issue a proposed rule within six months of its ANPRM (\textbf{by September 16, 2018}) and a final rule six months later (\textbf{by March 16, 2019}). We also urge that implementation of the rule be no later than the one-year period provided for in Section 907 of the Family Smoking Prevention and Tobacco Control Act, which would allow the rule to be implemented by \textbf{March of 2020}.”

\textbf{There is a compelling and urgent case for enacting promptly a national nicotine policy in the United States limiting cigarettes to minimally or non-addictive levels of nicotine.}
CONCLUSION

The FDA has clear authority under the Tobacco Control Act to promulgate a new rule that will require all cigarettes sold in the United States contain only minimally or non-addictive levels of nicotine. The FDA is pursuing the required rule-making process in a deliberative and thoughtful manner. In the interest of public health, the new nicotine rule should be enacted as promptly as possible.

The existence of 22nd Century’s VLNC SPECTRUM® research cigarettes proves that a product standard requiring a target of 0.5 +/- 0.2 mg nicotine content per gram of dry tobacco filler is immediately feasible. 22nd Century’s recent acquisition of additional VLN™ tobacco varieties adds to 22nd Century’s portfolio of VLN™ tobaccos available to produce cigarettes compliant with a new reduced nicotine standard. 22nd Century’s willingness to license the Company’s VLN™ tobacco technology and VLN™ seeds to any company eliminates any barriers to adoption of the technology.

The numerous peer-reviewed and published, independent clinical studies conducted with VLNC cigarettes made from 22nd Century’s VLN™ tobacco provide a solid scientific foundation for the FDA’s proposed new nicotine reduction rule. The FDA has stated that it will be led by the science in this important area... and the science has shown a clear path forward in the adoption of cigarettes made from tobacco containing minimally or non-addictive levels of nicotine.
Finally, and most importantly, the prompt implementation of the new product standard limiting the nicotine content in cigarettes is vital for the protection of public health. It is imperative that the FDA promptly issue a final rule to require that all cigarettes sold in the U.S. contain only minimally or non-additive levels of nicotine; only then will smokers no longer be subject to the robbery of choice that defines addiction.

Respectfully submitted,

By: Juan Pablo Sanchez Tamburrino, Ph.D.
Vice President of Research and Development
22nd Century Group, Inc.

Attachments: Completed Clinical Studies Using VLNC Cigarettes
On-Going Clinical Studies Using VLNC Cigarettes
1 https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm


4 Benowitz et al. “Reducing the nicotine content to make cigarettes less addictive,” Tobacco Control. April 15, 2013. https://tobaccocontrol.bmj.com/content/22/suppl_1/i14#ref-19


6 FDCA Section 911(b)(2)(A)(ii).

7 Vermont Center on Behavior and Health’s 5th Annual Conference on Tobacco Regulatory Science – October 5, 2017.


11 Hatsukami et al., 2010. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction. 105:343-355.

12 Smith et al., 2018. Impact of smoking reduced nicotine content cigarettes on sensitivity to cigarette price: further results from a multi-cite clinical trial. Addiction 112(2):349-359


14 Dermody et al., 2016. The impact of smoking very low nicotine content cigarettes on alcohol use. Alcohol Clin Exp Res. 40(3):606-615


17 “A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes.” (https://clinicaltrials.gov/ct2/show/NCT03571724)


19 https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm
Published Independent Clinical Studies Using Very Low Nicotine (VLN) Cigarettes:

1. Phase II – 136 Subjects
   Reduced Nicotine Content Cigarettes and Use of Alternative Nicotine Products: Exploratory Trial.
   University of Minnesota Masonic Cancer Center
   - There were higher rates of abstinence when smoking VLNC cigarettes compared with the normal nicotine condition
   - The offer of, and instructions to use, reduced nicotine content cigarettes over an 8 week period led to greater reductions in smoking rates
   - Funded by National Cancer Institute, and U.S. Food and Drug Administration (grant id: U19CA157345)

2. Phase II / III – 242 Subjects
   Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes
   Department of Medicine, University of California, San Francisco
   - Despite high levels of non-compliance, smokers reduced their intake of nicotine by an average of 60% after smoking only VLN cigarettes for six weeks
   - After six weeks of smoking VLN cigarettes, self-reported dependence and daily nicotine intake were lower at the end of the trial compared to the control condition
   - Funded by the National Institute on Drug Abuse (NIDA) and FDA Center for Tobacco Products (CTP) (grant id: U54 DA031659) and the National Cancer Institute (NLB) (grant id: R01 CA78603)

3. Phase II / III – 717 Subjects
   Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use.
   Duke University
   Pacek et al. – August 2016, *Drug & Alcohol Dependence*. DOI: 10.1016/j.drugalcdep.2016.08.620
   - Nicotine reduction in cigarettes could have beneficial effects on cigarette smoking regardless of cannabis use
   - Among cannabis users and non-users, smokers randomized to VLNC cigarettes reported lower nicotine dependence, cigarettes per day, biomarkers of nicotine
exposure, and craving compared to smokers randomized to normal nicotine content cigarettes

- Funded by the National Institute on Drug Abuse and FDA Center for Tobacco Products (grant id: U54 DA031659)

4. Phase II / III – 717 Subjects

**Effects of 6-Week Use of Reduced-Nicotine Content Cigarettes in Smokers With and Without Elevated Depressive Symptoms.**

Center for Alcohol and Addiction Studies, Brown University


- Relative to normal nicotine level cigarettes, VLN cigarettes reduced smoking rates, nicotine dependence and cigarette craving.
- These findings provide initial evidence that a reduced-nicotine standard for cigarettes may reduce smoking, without worsening depressive symptoms, among smokers with elevated depressive symptoms.
- Funded by the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products (grant id: U54DA031659)

5. Phase II – 168 Subjects

**A Randomized Controlled Trial of Progressively Reduced Nicotine Content Cigarettes on Smoking Behaviors, Biomarkers of Exposure, and Subjective Ratings**

Department of Psychiatry, University of Pennsylvania


- The lowest reduced nicotine level cigarette tested (0.05 mg nicotine yield) may reduce harm exposure
- Use of VLN cigarettes decreased daily consumption, as well as nicotine and toxicant exposure, relative to use of moderate nicotine content cigarettes
- Funded by the National Institutes of Health

6. Phase II – 200 Subjects

**Complementing the Standard Multicomponent Treatment for Smokers With Denicotinized Cigarettes: A Randomized Trial.**

Queen Mary University, London


- The group that used VLN cigarettes had a 70% quit rate one week after stopping VLN cigarette use compared to a 53% quit rate of the group not using VLN cigarettes
Adding VLN cigarettes to standard treatments has the potential to assist smokers early in their quit attempt, but research is needed to determine how best to utilize VLNs.

- Funded by Pfizer, Inc.

7. Phase II / III – 839 Subjects

**The Impact of Smoking Very Low Nicotine Content Cigarettes on Alcohol Use.**

Department of Psychology, University of Pittsburgh


- A reduced nicotine product standard could positively impact related health risk behaviors like drinking
- Compensatory drinking is unlikely to occur in response to switching to VLN cigarettes and reducing the nicotine content of cigarettes may reduce alcohol consumption
- Funded by the National Institute on Drug Abuse and FDA Center for Tobacco Products (CTP) (grant id: U54 DA031659) and National Institute on Alcohol Abuse and Alcoholism (grant id: F31AA022291)

8. Phase I – 50 Subjects

**Smoking Topography Characteristics of Very Low Nicotine Content Cigarettes, With and Without Nicotine Replacement, in Smokers With Schizophrenia and Controls**

Center for Alcohol and Addiction Studies, Brown University


- Acute use of VLN cigarettes does not increase intensity of smoking in schizophrenics and this supports the feasibility of a nicotine reduction policy
- During VLN cigarette sessions, puff duration increased and time between puffs decreased, but participants smoked fewer puffs, resulting in a net decrease in cigarette and total session volume
- Funded by the National Institute on Drug Abuse (NIDA)

9. Phase II / III – 840 Subjects

**Randomized Trial of Reduced-Nicotine Standards for Cigarettes**

University of Pittsburgh


- Participants who were assigned VLN cigarettes smoked fewer cigarettes per day (14.9) than those assigned to their usual brand (22.2)
- Smokers of VLN cigarettes doubled their quit attempts versus smokers of conventional cigarettes
10. Phase II – 112 Subjects

**Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation**
Department of Psychology, University of Pittsburgh
- Reducing the nicotine content of cigarettes is a potential regulatory strategy that may enable cessation
- When smoking Very Low Nicotine cigarettes, lower levels of nicotine exposure prior to a quit attempt enables cessation
- Funded by the National Institutes of Health (NIH), (grant id: R01 DA025598 and U54DA031659)

11. Phase II – 219 Subjects

**Reduced Nicotine Content Cigarettes and Nicotine Patch – Follow-up Study**
University of Minnesota Masonic Cancer Center
- VLN cigarettes produced significantly better results than FDA-approved nicotine lozenges; even those smokers who ultimately didn’t quit ended up reducing their cigarette consumption from 19 cigarettes per day to 12 cigarettes per day
- Very Low Nicotine cigarettes were associated with greater relief of withdrawal than the nicotine lozenge
- Funded by the National Institutes of Health (NIH), (grant id: R01 DA025598 and U54DA031659)

12. Phase III – 1,410 Subjects

**The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial.**
Clinical Trials Research Unit, University of Auckland
- VLN cigarettes plus NRT (nicotine patch, gum and/or lozenge) significantly increased quit rates at all measured time points (3 & 6 weeks and 3 & 6 months) over use of NRT only
• Addition of very low nicotine content cigarettes to standard Quitline smoking cessation support may help some smokers to become abstinent
• Funded by the Health Research Council of New Zealand

13. Phase II – 165 Subjects

Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation.
University of Minnesota Masonic Cancer Center
Hatsukami et al. – February 2010, Addiction. 105:343-355
• VLN cigarettes produced significantly better results than the FDA-approved nicotine lozenge; even the smokers who ultimately did not quit ended up reducing their cigarette consumption by 37%
• The 0.05 mg nicotine yield cigarettes may be a tobacco product that can facilitate cessation
• This study was funded by the National Institutes of Health (NIH), (grant id: P50 DA013333)

14. Phase II – 346 Subjects

A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation.
Department of Psychiatry & Behavioral Sciences, Duke University Medical Center
Becker et al. – July 2008, Nicotine & Tobacco Research. 10:1139-1148
• The use of reduced nicotine cigarettes for 6 weeks, including VLN cigarettes for 2 weeks, before the use of the nicotine patch significantly increased quit rates over use of the nicotine patch alone
• VLN cigarettes plus nicotine replacement therapy offers promise as a new smoking cessation treatment.
• Funded by Vector Tobacco Inc.

15. Phase II – 98 Subjects

Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings?
Roswell Park Cancer Institute
Rezaishiraz et al. – November 2007, Nicotine & Tobacco Research. 9:1139-1146
• Use of VLN cigarettes before use of nicotine patches increased quit rates over similar use of reduced nicotine cigarettes (containing 10 times more nicotine than the VLN) before nicotine patches
• The use of a VLN cigarettes combined with the nicotine patch appears to lessen cravings to smoke in the immediate post cessation period
• Funded by institutional resources from Roswell Park Cancer Institute
On-Going Independent Clinical Studies Using VLN Cigarettes:

1. **Project 2: Strategies for Reducing Nicotine Content in Cigarettes**
   - ClinicalTrials.gov Identifier: [NCT02139930](https://clinicaltrials.gov/ct2/show/NCT02139930)
   - Sponsor: University of Pittsburgh
   - Collaborator: National Institute on Drug Abuse (NIDA)

2. **Facilitating Smoking Cessation With Reduced Nicotine Cigarettes**
   - ClinicalTrials.gov Identifier: [NCT02796391](https://clinicaltrials.gov/ct2/show/NCT02796391)
   - Sponsor: H. Lee Moffitt Cancer Center and Research Institute
   - Collaborator: James and Esther King Biomedical Research Program

3. **Novel Approaches to Reducing Tobacco Related Harm**
   - ClinicalTrials.gov Identifier: [NCT02600273](https://clinicaltrials.gov/ct2/show/NCT02600273)
   - Sponsor: Duke University
   - Collaborator: National Institute of Allergy and Infectious Diseases (NIAID)

4. **Abuse Liability of Reduced Nicotine Content Cigarettes in the Context of Concurrent E-Cigarette Use**
   - ClinicalTrials.gov Identifier: [NCT02870218](https://clinicaltrials.gov/ct2/show/NCT02870218)
   - Sponsor: Rose Research Center, LLC
   - Collaborators: National Institutes of Health (NIH) and Food and Drug Administration (FDA)

5. **Effects of Nicotine Reduction on Smoking Behavior in ADHD Smokers**
   - ClinicalTrials.gov Identifier: [NCT02599571](https://clinicaltrials.gov/ct2/show/NCT02599571)
   - Sponsor: Duke University
   - Collaborators: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Food and Drug Administration (FDA), and University of Pittsburgh

6. **Evaluation of Very Low Nicotine Content Cigarettes in Adolescent Smokers**
   - ClinicalTrials.gov Identifier: [NCT02587312](https://clinicaltrials.gov/ct2/show/NCT02587312)
   - Sponsor: Brown University
   - Collaborator: National Cancer Institute (NCI)

7. **Manipulating Tobacco Constituents in Female Menthol Smokers**
   - ClinicalTrials.gov Identifier: [NCT02048852](https://clinicaltrials.gov/ct2/show/NCT02048852)
8. **Manipulating Tobacco Constituents in Male Menthol Smokers**  
   ClinicalTrials.gov Identifier: [NCT02592772](https://clinicaltrials.gov/ct2/show/NCT02592772)  
   Sponsor: University of Connecticut Health Center  
   Collaborator: National Institute on Drug Abuse (NIDA)

9. **Project 1, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Childbearing Age Women**  
   ClinicalTrials.gov Identifier: [NCT02250534](https://clinicaltrials.gov/ct2/show/NCT02250534)  
   Sponsor: University of Vermont  
   Collaborators: National Institute on Drug Abuse (NIDA) and Johns Hopkins University

10. **Project 1, Study 2: The Combined Impact of Nicotine Replacement and Spectrum Cigarettes**  
    ClinicalTrials.gov Identifier: [NCT02301325](https://clinicaltrials.gov/ct2/show/NCT02301325)  
    Sponsor: University of Pittsburgh

11. **Project 2, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Opioid Abusers**  
    ClinicalTrials.gov Identifier: [NCT02250664](https://clinicaltrials.gov/ct2/show/NCT02250664)  
    Sponsor: University of Vermont  
    Collaborators: National Institute on Drug Abuse (NIDA) and Johns Hopkins University

12. **Project 3, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in People With Current Affective Disorders**  
    ClinicalTrials.gov Identifier: [NCT02232737](https://clinicaltrials.gov/ct2/show/NCT02232737)  
    Sponsor: Brown University  
    Collaborator: University of Vermont

13. **Reduced Nicotine Content Cigarettes in Smokers of Lower Socioeconomic Status**  
    ClinicalTrials.gov Identifier: [NCT01928719](https://clinicaltrials.gov/ct2/show/NCT01928719)  
    Sponsor: Milton S. Hershey Medical Center  
    Collaborator: George Washington University

14. **Reduced Nicotine Cigarettes in Smokers With Mood and Anxiety Disorders**  
    ClinicalTrials.gov Identifier: [NCT01928758](https://clinicaltrials.gov/ct2/show/NCT01928758)
15. **Strengthening Instrumental Extinction to Prevent Smoking Relapse (VLNCCue)**
   - ClinicalTrials.gov Identifier: [NCT02538042](https://clinicaltrials.gov/ct2/show/NCT02538042)
   - Sponsor: Francis McClernon
   - Collaborators: National Institutes of Health (NIH) and National Institute on Drug Abuse (NIDA)

16. **Switching to Reduced Oxidant or Nicotine Content Cigarettes in Smokers**
   - ClinicalTrials.gov Identifier: [NCT02415270](https://clinicaltrials.gov/ct2/show/NCT02415270)
   - Sponsor: Milton S. Hershey Medical Center
   - Collaborators: Food and Drug Administration (FDA), National Institutes of Health (NIH), and National Institute on Drug Abuse (NIDA)

17. **Very-Low Nicotine Cigarettes and Non-Daily Smokers**
   - ClinicalTrials.gov Identifier: [NCT02228824](https://clinicaltrials.gov/ct2/show/NCT02228824)
   - Sponsor: University of Pittsburgh
   - Collaborator: National Cancer Institute (NCI)

18. **Very Low Nicotine Cigarettes in Smokers With Schizophrenia**
   - ClinicalTrials.gov Identifier: [NCT02019459](https://clinicaltrials.gov/ct2/show/NCT02019459)
   - Sponsor: Brown University
   - Collaborators: National Institute on Drug Abuse (NIDA) and University of Pittsburgh

19. **Very Low-Nicotine Cigarettes in Smokers With SUD**
   - ClinicalTrials.gov Identifier: [NCT01989507](https://clinicaltrials.gov/ct2/show/NCT01989507)
   - Sponsor/Collaborator: Brown University

20. **Neuroimaging Reward, Behavioral Treatment, and Smoking Cessation**
    - ClinicalTrials.gov Identifier: [NCT02927847](https://clinicaltrials.gov/ct2/show/NCT02927847)
    - Sponsor: Maggie M. Sweitzer, PhD
    - Collaborator: National Institute on Drug Abuse (NIDA)

21. **Abuse Liability of Reduced Nicotine Content Cigarettes Within a Complex Tobacco Marketplace: Experiment 1**
    - ClinicalTrials.gov Identifier: [NCT02951143](https://clinicaltrials.gov/ct2/show/NCT02951143)
    - Sponsor: Virginia Polytechnic Institute and State University
22. Concomitant Use of Very Low Nicotine Content Cigarettes and e-Cigarettes
   ClinicalTrials.gov Identifier: NCT02964182
   Sponsor: M.D. Anderson Cancer Center
   Collaborator: National Institute on Drug Abuse (NIDA)

23. Reactions to Reduced Nicotine Cigarettes in Young Adult Low-Frequency Smokers (NicRed)
   ClinicalTrials.gov Identifier: NCT02989038
   Sponsor: Duke University
   Collaborator: National Institute on Drug Abuse (NIDA)

24. Reduced Nicotine Cigarettes in Smokers With and Without Alcohol Use Disorder (RedNic)
   ClinicalTrials.gov Identifier: NCT02990455
   Sponsor: Battelle Memorial Institute

25. Switching to Very Low Nicotine Content Cigarettes vs Reducing Cigarettes Per Day
   ClinicalTrials.gov Identifier: NCT03060083
   Sponsor: University of Vermont

26. 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

27. Evaluation of the Abuse Liability of Very Low Nicotine (VLN) Cigarettes
   ClinicalTrials.gov Identifier: NCT03559751
   Sponsor: 22nd Century Group, Inc.
   Collaborator: Vince & Associates Clinical Research, Inc.

28. Evaluation of Abuse Liability of Very Low Nicotine (VLN) Mentholated Cigarettes
   ClinicalTrials.gov Identifier: NCT03559725
   Sponsor: 22nd Century Group, Inc.
   Collaborator: Vince & Associates Clinical Research, Inc.
Commentaries and Opinion Pieces:

1. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game.  
   Benowitz et al. – August 2016, Addiction. DOI: 10.1111/add.13534

2. Let actual markets help assess the worth of optional very-low-nicotine cigarettes before deciding on mandatory regulations.  
   Kozlowski et al. – August 2016, Addiction. DOI: 10.1111/add.13515

3. Paying more attention to the 'elephant in the room'.  
   Borland et al. – June 2016, Tobacco Control. DOI: 10.1136/tobaccocontrol-2016-053150

4. The case for the WHO Advisory Note, Global Nicotine Reduction Strategy.  
   Hatsukami et al. – June 2016, Tobacco Control. DOI: 10.1136/tobaccocontrol-2016-053134

5. Randomized Trial of Reduced-Nicotine Standards for Cigarettes.  

6. Randomized Trial of Reduced-Nicotine Standards for Cigarettes.  

7. Randomized Trial of Reduced-Nicotine Standards for Cigarettes.  

8. Randomized Trial of Reduced-Nicotine Standards for Cigarettes.  

9. Reduced-Nicotine Cigarettes — A Promising Regulatory Pathway  

10. Nicotine Reduction: Strategic Research Plan  
    Hatsukami et al. – June 2012, Nicotine & Tobacco Research. 15:1003-13