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Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
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Silver Spring, MD 20993-0002

RE: Modified Risk Tobacco Products Application Renewal for MR0000159 – MR0000160

22nd Century Group, Inc. (“22nd Century Group”) submits this Modified Risk Tobacco Products Application (“MRTPA”) renewal under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”) to renew 22nd Century Group’s Modified Risk Granted Orders – Exposure Modification (“MRGOs”) for two (2) VLN[®] Reduced Nicotine Content cigarette products¹ manufactured by NASCO Products, LLC, a wholly owned subsidiary of 22nd Century

¹ On December 17, 2019, FDA issued marketing granted orders for the Products (PM0000491-PM0000492) under the PMTA pathway after finding the Products meet the criteria specified in section 910(c) of the FD&C Act.

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Group, with Submission Tracking Numbers MR0000159-MR0000160 (“the Products”) issued on December 23, 2021, with the following authorized claims and required condition of use:

Primary Authorized Claims:

1. **“95% less nicotine”**
2. **“Helps reduce your nicotine consumption”**
3. **“...greatly reduces your nicotine consumption”**

Required Condition of Use:

1. **“Helps you smoke less”**

In its Orders, the U.S. Food and Drug Administration (“FDA”) also recommended the product label, labeling, or advertising (“LLA”) include the following disclaimer: “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death” (“the Disclaimer”). However, in a letter to the FDA dated December 1, 2023, 22nd Century Group confirmed to the FDA that it would remove the Disclaimer for all LLA and has since removed the Disclaimer from VLN[®] LLAs.

In the Orders, the FDA stated that 22nd Century Group’s MRTPAs **“... [s]atisfied the requirements of section 911(g)(2)(A) and (B), including that they are appropriate to promote the public health and are expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.”**

VLN[®] cigarettes’ Orders remain appropriate for the protection of public health (“APPH”) as evidenced by 22nd Century Group’s periodic reporting, external studies conducted by independent researchers, and ongoing postmarket surveillance and studies (“PMSS”). Furthermore, the following conclusions remain valid:

1. VLN[®] cigarettes contain 95% less nicotine, with a target of 0.5mg/g on a dry weight basis, and help adult smokers smoke less.
2. Independent studies conducted since the Orders’s issuance and 22nd Century Group’s ongoing PMSS show that adult consumers continue to understand the claims authorized under the Orders and are not misled by 22nd Century Group’s LLAs

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3. VLN[®]'s commercial introduction has not caused an increase in initiation of tobacco use by non-users, an increase in youth initiation, or an increase in compensatory cigarette or nicotine use by adult smokers.

In subsequent sections, 22nd Century Group will expand on the conclusions above, with both data submitted with 22nd Century Group's original submission and subsequent periodic reports.

22nd Century Group also notes that no substantial concerns have been brought to 22nd Century's attention related to the VLN[®] products' APPH findings from information provided by 22nd Century Group since the Orders were issued in 2021. Therefore, FDA should grant the renewal of the Orders.

Finally, this MRTPA renewal contains non-public, trade secret, and confidential commercial information throughout. This information belongs to 22nd Century Group or its suppliers and is exempt from public disclosure. 22nd Century Group understands that the FDA is required to make this MRTPA renewal public and, in order to facilitate publication of the portions that are not non-public, trade secret, or otherwise confidential commercial information, a redacted version is also submitted by 22nd Century Group identifying the portions exempt from public disclosure. In the event that any information that has been identified or designated as confidential by 22nd Century Group is considered non-confidential by the FDA, the Company requests that the FDA provide pre-disclosure notice to 22nd Century Group pursuant to the procedures set forth in 21 C.F.R §20.61(d) and (e). 22nd Century Group appreciates the FDA's consideration of this MRTPA renewal and welcomes the opportunity to discuss with the FDA any questions it may have. 22nd Century Group looks forward to working with the FDA to renew its Orders under 911(g)(2) of the FD&C Act for the subject products discussed herein and in the attached MRTPA renewal.

Sincerely,

(b) (6)

Jonathan Staffeldt

General Counsel

22nd Century Group, Inc

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1. EXECUTIVE SUMMARY

22nd Century Group submits this application to renew FDA’s Modified Risk Granted Orders – Exposure Modification issued December 23, 2021, for two (2) VLN® Reduced Nicotine Content (“RNC”) cigarette products (see **Table 1**) under section 911 of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”).

FDA’s MRGOs authorized 22nd Century Group to use the following modified exposure claims in the Products’ label, labeling, or advertising:

1. “95% less nicotine”
2. “Helps reduce your nicotine consumption”
3. “...greatly reduces your nicotine consumption”

When authorized modified exposure claims are used in the Products’ LLA, FDA required the following condition of use: “Helps you smoke less.”

In its Orders, the FDA also recommended the LLA include the following disclaimer: “Nicotine is addictive. Less nicotine does not NOT mean safer. All cigarettes can cause disease and death” (“the Disclaimer”). However, in a letter to the FDA dated December 1, 2023, 22nd Century Group confirmed to the FDA that it would remove the Disclaimer for all LLA and has since removed the Disclaimer from VLN® LLAs.

In its MRGOs, the FDA concluded that the Products “...[h]ave satisfied the requirements of section 911(g)(2)(A) and (B), including that they are appropriate to promote the public health and are expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.”

FDA’s conclusions remain true and the reasoning that supported FDA’s orders under the Premarket Tobacco Product Application (“PMTA”) and Modified Risk Tobacco Product Application pathways remains valid today. These Products, with their authorized Modified Risk Tobacco Product (“MRTP”) claims, continue to be appropriate for the protection of public health. Furthermore, FDA has not expressed any concerns regarding the information 22nd Century Group provided about the MRTPs being APPH. Therefore, FDA should renew each MRGO based on the following outlined information.

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1.1. VLN[®] RNC Cigarettes' Marketing Granted Orders Summary

The Products remain APPH under the PMTA pathway. On December 17, 2019, FDA issued marketing granted orders (“MGOs”) for the Products (PM0000491-PM0000492) under the PMTA pathway after finding the Products meet the criteria specified in section 910(c) of the FD&C Act. FDA’s reasons for issuing the MGOs included the following:

- While the overall toxicant-associated noncancer hazards and cancer risks due to use of the Products are likely similar to the application’s six comparator normal nicotine content (“NNC”) cigarettes, assuming that the Products are used in the same way as the comparators, these hazards and risks of use of the Products could be lower than use of the NNC cigarettes based on patterns of use (decreased cigarettes per day and puffing volume) exhibited by users of very low nicotine content (“VLNC”) cigarettes that were very similar to the Products.
- The pharmacokinetic profile of the Products indicates a lower abuse liability than the application’s usual brand-normal nicotine content (“UB-NNC”) cigarette comparator.
- The Products are associated with lower positive subjective effects ratings (e.g., liking, pleasant, satisfaction) compared to UB-NNC cigarettes, reducing their abuse liability for youth and non-smokers.
- Menthol and non-menthol NNC smokers who choose to switch to cigarettes like the Products would experience the benefit of significantly reducing their overall exposure to nicotine, potentially reducing their overall smoking, and subsequently, their exposure to non-nicotine harmful and potentially harmful constituents (“HPHCs”). Given that current adult smokers are the intended population for the Products, reduced likelihood of use among adult smokers is likely to reduce youth access to these products and their availability for youth experimentation.
- Youth who experiment with cigarettes like the Products may find them less appealing and may be less likely to develop nicotine dependence and become established cigarette smokers due to their lower abuse liability profile.

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- Switching to cigarettes like the Products may facilitate abstinence in smokers by increasing motivation to quit and quit attempts. Concurrent use of NRT and behavioral intervention may improve these outcomes.

1.2. VLN[®] RNC Cigarettes' Modified Risk Granted Orders Summary

The Products remain APPH under the MRTPA pathway. On December 23, 2021, FDA issued MRGOs to the modified risk tobacco products (MR0000159-MR0000160) under the MRTPA pathway, after finding the Products satisfied the requirements of Section 911(g)(2)(A) and (B) of the FD&C Act. FDA's reasons for granting the MRGOs included:

- The reported nicotine contents of the Products are 98% lower than the average reported nicotine contents of the top 100 cigarette brands determined both per gram of tobacco and per cigarette. In addition, both applicant-contracted and FDA nicotine test results found that nicotine levels in tobacco and mainstream smoke of the Products are at least 96% lower than the majority of marketed and market-leading conventional cigarette brands.
- The unique tobacco used in the Products contains at least 95% less nicotine than the reported nicotine content for conventional cigarette tobacco.
- By exclusively smoking VLNC cigarettes like the Products, consumers could reduce their exposure to nicotine by approximately 95%.
- Menthol and non-menthol smokers who primarily smoke the Products and occasionally dual use, with other tobacco or nicotine-containing products, still experience the benefit of substantially reducing their overall exposure to nicotine compared to exclusively smoking UB-NNC cigarettes.
- While the Products may expose some smokers to higher levels of some HPHCs, such increases are minimal; the reasonably likely overall impact of use remains a substantial reduction in morbidity among tobacco users.
- The abuse liability of the Products is low based on plasma nicotine levels after using them and low subjective effects ratings.
- It is reasonably likely that cigarette smokers who use the Products will experience a reduction in nicotine dependence, which will also reduce tobacco dependence. Reductions in tobacco dependence can lead to increased tobacco cessation and are

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anticipated to lead to long-term reductions in exposure to the smoking-related toxicants associated with morbidity and mortality.

- Testing of actual consumer perceptions shows that, overall, consumer understanding is generally in line with the health risks of the Products that are reasonably likely and the current state of the evidence.

As a condition of the MRGOs, 22nd Century Group was required to conduct postmarket surveillance and studies (“PMSS”) per Section 911(g)(2)(C)(ii) of the FD&C Act. In recent a communication to the FDA, 22nd Century Group informed the FDA that its PMSS, including cross-sectional study (b) (4) (“CS”) and longitudinal study (b) (4) (b) (4) (“LS”) were in process. The CS is now complete and an update in the form of a report was provided to the FDA on Tuesday, December 23, 2025. The LS is projected to be complete in February 2027, and 22nd Century Group will provide an update to FDA as appropriate.

Since the MRGOs’ issuance on December 23, 2021, 22nd Century Group has complied with all FDA requirements including, but not limited to, LLA, sales data, ongoing and completed studies, and adverse event reporting. 22nd Century Group’s continued compliance reinforces the fact that 22nd Century Group’s RNC cigarettes subject to MRGO renewal remain APPH. FDA has not raised concerns about the Products not being APPH since its issuance of the MRGOs in 2021 and, therefore, the conclusions that supported the initial MRGOs remain valid and support the renewal of the MRGOs.

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2. TOBACCO PRODUCTS SUBJECT TO MRTPA RENEWAL

Table 1: MRTP Products Subject to Renewal

Product Name	Product Category	Product Subcategory	Product Submission Tracking Numbers
VLN King	Cigarettes	Combusted, Filtered	PM0000491, MR0000159
VLN Menthol King	Cigarettes	Combusted, Filtered	PM0000492, MR0000160

3. SUMMARY OF SCIENTIFIC EVIDENCE

All information submitted with the original MRTPA’s for both the Products remains valid and continues to support FDA’s initial rationale for issuing the MRGOs. The following section provides an overview and discussion of internal and external data pertaining to 22nd Century Group’s Products since FDA’s initial issuance of the MRGOs. In light of the discussion below, 22nd Century Group reiterates its intention to renew all of the Submission Tracking Numbers listed in Table 1. Maintaining the only low nicotine combustible options with MRGOs will benefit intended adult consumers who want to smoke fewer combustible cigarettes.

3.1. Relative Health Risks of the MRTPs to Individual Tobacco Users

Nicotine is the primary driver of cigarette addiction, and its effects make quitting especially difficult. Over time, the body becomes accustomed to regular nicotine intake, creating dependence that triggers strong cravings. These physiological responses, combined with ingrained habits and emotional cues, can make quitting challenging even for people who are highly motivated. This struggle is not about willpower; it reflects how nicotine acts on the brain to reinforce continued use. As the FDA notes, “nicotine has been extensively studied and the evidence overwhelmingly demonstrates that nicotine is an addictive drug and the fundamental reason that individuals continue using tobacco products.”

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Our initial PMTA and MRTPA submissions included scientific evidence demonstrating that consumers who switched to VLNC cigarettes smoked fewer cigarettes and made more quit attempts than those who used NNC cigarettes. In the 4 years since receiving the MRGOs, a growing body of independent research directly examining VLNC products has continued to support these conclusions.

The FDA’s peer-reviewed scientific assessment evaluated how lowering nicotine levels in combusted tobacco products affects smoking behavior, dependence, toxicant exposure, and public understanding of nicotine and VLNC cigarettes. According to the review, “the totality of the evidence supports that extended exposure to combusted cigarettes containing VLNC tobacco filler is associated with reduced addiction potential, dependence levels, and number of cigarettes smoked per day, and increased quit attempts among people who currently smoke cigarettes, without evidence of increased toxicant exposure, craving, withdrawal, or compensatory smoking.” In short, the FDA’s 2025 peer-reviewed scientific assessment indicates that VLNC cigarettes can meaningfully reduce dependence and encourage cessation without introducing new health risks or prompting harmful compensatory behaviors.²

Taken together, the peer-reviewed scientific assessment by the FDA, internal peer-reviewed annual reports, and data from 22nd Century Group’s original PMTAs and MRTPAs, support the conclusions made in the original applications: (1) VLNC cigarettes significantly reduce nicotine exposure; and (2) providing smokers who would otherwise continue smoking with a very low nicotine combustible cigarette can lessen nicotine dependence and may help facilitate quitting or reducing cigarette consumption. Despite the available evidence, 22nd Century Group’s MRTPA did not seek smoking cessation claims, and 22nd Century does not seek to change that position at this time.

The FDA’s position on reducing nicotine content across all combustible cigarettes aligns with that of 22nd Century Group. Both maintain that lowering nicotine to minimally addictive or non-addictive levels can help people smoke fewer combustible cigarettes. 22nd Century Group

² Food and Drug Administration. (2023). Tobacco product standard for nicotine level of cigarettes (Proposed rule). Federal Register, 88, 950–1047. <https://www.federalregister.gov/documents/2023/01/13/2023-00536/tobacco-product-standard-for-nicotine-level-of-cigarettes>

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continues to agree with the FDA that nicotine reduction is a key strategy for decreasing smoking-related disease and death.

Further evidence includes the following:

- No serious or adverse experiences bringing into question whether the Products MRGOs remain APPH were reported for PM0000491/MR0000159 – PM0000492/MR0000160.
- 22nd Century Group does not make direct-to-consumer sales of VLN® cigarettes. Information on 22nd Century Group’s responsible marketing practices can be found in Appendices of each MRGO periodic report.
- No manufacturing deviations were reported for PM0000491/MR0000159 – PM0000492/MR0000160. There has been no change to the manufacturing facility or controls due to the production of PM0000491/MR0000159 – PM0000492/MR0000160 from 2019 to 2025. The Products continue to remain appropriate for the protection of public health and, therefore, should retain their MRGOs via an MRTPA renewal.
- The low nicotine standard of 0.3-0.7mg/g remains well adhered to as evidenced by the results from our extensive routine testing. Thus, consumers who either continue to use VLN® cigarettes or switch from other NNC cigarettes would be exposed to 95% less nicotine.

3.2. Consumer Understanding and Perceptions

Qualitative evidence gathered across peer-reviewed research studies completed post-MRGOs demonstrate consistent consumer comprehension of the reduced nicotine message associated

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with VLNC cigarettes. These findings indicate that consumers generally understand the intent of the reduced nicotine claim, as well as the continuing risks of smoking these products.^{3,4}

According to the CS study commissioned as part of the PMSS requirement and submitted with 22nd Century Group’s 2025 annual/periodic MRGO/MGO report, consumer responses indicate that the overwhelming majority of VLN® cigarette users were existing adult cigarette smokers and they understood key aspects of nicotine addiction and the continued health risks associated with smoking. The majority recognize that nicotine is addictive and that all cigarette smoke, including VLN® smoke, contains toxic chemicals. Most users also understand that cigarette smoke, rather than nicotine itself, is responsible for serious health harms, and many acknowledge that all cigarettes, including VLN® products, can cause disease and death. Users widely report that VLN® cigarettes are intended to help reduce smoking frequency and duration. While there were some uncertainties among certain consumer responses as to whether VLN® products are less harmful than NNC cigarettes, the perception study did not raise any new questions about the authorized claims than our original MRTPA highlighted.

In recent public comments, FDA indicated its desires to improve public communications on the subjects of nicotine and Tobacco Harm Reduction (“THR”). 22nd Century Group is committed to working alongside the FDA to help improve public understanding of VLNC cigarettes and their role in THR. Through clear, science-based communication and coordinated educational efforts, we aim to aid the agency’s mission to correct misconceptions and misperceptions, to ensure consumers have reliable information about the risks, limitations, and intended purpose of these products.

3.3. Tobacco Use Behavior and Impact to the Population as a Whole

³ DeAtley T, Harrison A, Cassidy R, Kuo C, Higgins ST, Tidey JW. Subjective experiences, contexts, and risk perceptions of very low nicotine content cigarettes and electronic cigarettes among people with depression and anxiety disorders who smoke. *Drug Alcohol Depend.* 2023;244:109767. doi:10.1016/j.drugalcdep.2023.109767

⁴ Tan ASL, Mercincavage M, Young WJ, Hrywna M, Delnevo CD, Strasser AA. Perceived relative harm and addictiveness compared with cigarettes and intentions to use modified risk tobacco products utilizing FDA-authorized marketing claims among adults in the United States. *Drug Alcohol Depend.* 2024;261:111291. doi:10.1016/j.drugalcdep.2024.111291

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Extensive evidence demonstrates that VLNC cigarettes drastically reduce smokers' nicotine exposure compared to NNC cigarettes. Studies have consistently shown lower plasma cotinine levels and lowered exhaled carbon monoxide compared to NNC cigarettes, indicating a decrease in exposure to nicotine and decreased cigarette consumption. No significant differences in exposure were observed across demographic subgroups, indicating that the benefits of nicotine reductions are consistent and in alignment with the original PMTAs and MRTPA^s.^{5,6,7,8} Independent research studies consistently illustrate that smokers who smoke VLNC cigarettes cut down on their cigarette consumption per day, and, from an abuse liability perspective, VLNC cigarettes were found to be less reinforcing when compared to smokers' regular brand of cigarettes, underscoring the limited addictive potential of VLN® products.^{7,9,10,11} In practical terms, offering 95% less nicotine combustible cigarettes helps smokers smoke less. By markedly reducing nicotine dependence, VLNC cigarettes continue to serve as a steppingstone for smokers toward quitting or switching from combustible cigarettes to lower-risk nicotine sources.

To more comprehensively understand how these effects manifest in a real-world setting, one recent and highly relevant intervention study evaluated tobacco and nicotine delivery usage by a

⁵ Bello MS, Wang CX, Maglalang DD, Rosales R, Tidey JW, Denlinger-Apte RL, Sokolovsky AW, Colby SM, Cassidy RN. Racial/ethnic differences in the acute effects of reduced nicotine content cigarettes among adolescents who smoke. *Addict Behav.* 2025;160:108147. doi:10.1016/j.addbeh.2024.108147

⁶ Smith TT, Luo X, Benowitz NL, Colby SM, McClernon FJ, Strasser AA, Tidey JW, Donny EC, Hatsukami DK. The impact of nicotine reduction on cigarette reinforcement value within a marketplace containing alternative nicotine delivery products: a secondary analysis of a multi-site trial. *Nicotine Tob Res.* 2025. doi:10.1093/ntr/ntaf138

⁷ Cassidy RN, Tidey JW, Bello MS, Denlinger-Apte R, Goodwin C, Godin J, Cioe PA, Swift R, Demorest C, Koopmeiners JS, Donny EC, Hatsukami D, Colby SM. Effects of very low nicotine content cigarettes and nicotine vaping device characteristics on choices to smoke, vape, or abstain in early young adults. *Nicotine Tob Res.* 2024;27:244-253. doi:10.1093/ntr/ntae194 (NOTE: 22nd Century Group does not market tobacco products to persons not of legal smoking age and does not condone underage smoking.)

⁸ Lin W, Krebs NM, Zhu J, Horn K, Foulds J, Evins AE, Muscat JE. Racial differences in nicotine reduction: pooled results from two double-blind randomized controlled trials. *J Racial Ethn Health Disparities.* 2024. doi:10.1007/s40615-024-02155-1

⁹ Hatsukami DK, Luo X, Jensen J, et al. Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. *JAMA.* 2018;320(9):880-891. doi:10.1001/jama.2018.11473

¹⁰ Klemperer EM, Luo X, Jensen J, et al. Smoking abstinence and cessation-related outcomes one month after an immediate versus gradual reduction in nicotine content of cigarettes. *Prev Med.* 2022;165(Pt B):107175. doi:10.1016/j.ypmed.2022.107175

¹¹ Hatsukami DK, Jensen JA, Carroll DM, et al. Reduced nicotine in cigarettes in a marketplace with alternative nicotine systems: randomized clinical trial. *Lancet Reg Health Am.* 2024;35:100796. doi:10.1016/j.lana.2024.100796

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group of smokers free to supplement their existing NNC cigarette usage with a representative array of marketplace alternatives (including e-cigarettes, smokeless tobacco, and medicinal nicotine) as compared to a control group required to use only VLNC cigarettes (the “2024 Marketplace Study”).¹¹ After 12 weeks, based on voluntary behaviors alone, smokers with access to VLNC cigarettes smoked on average 45% fewer cigarettes per day and had more than triple the number of smoke-free days compared to those who retained access to NNC cigarettes. The VLNC cigarette group cut their overall cigarette consumption by more than half, despite being “predominantly not interested in quitting smoking” at the study outset. By comparison, those who continued use of NNC cigarettes barely reduced their cigarette consumption even though they had access to a full variety of reduced exposure smoking alternatives and cessation aids representative of the current marketplace.

Collectively, the results from independent research studies and the scientific evidence originally provided in the MRTPA substantiate the authorized MRTP claims and demonstrate that the Products’ MRGOs remain appropriate for the protection of public health.

4. LIST OF EXHIBITS

- Exhibit A** **PreMarket Tobacco Product Marketing Granted Order (“MGO”)**
- Exhibit B** **Modified Risk Granted Order (“MRGO”)**
- Exhibit C** **PDF Summary of Previous Periodic PMTA and MRTPA Reporting**

22nd Century Group incorporates, by reference, information from all previous PMTA and MRTPA applications and periodic reporting in this MRGO renewal request for STNs MR0000159 –MR0000160.

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This document contains confidential commercial information and trade secrets of 22nd Century Group, Inc., including proprietary scientific, technical, and commercial information, that are exempt from public disclosure pursuant to the Freedom of Information Act (5 U.S.C. § 552) and FDA regulations at 21 C.F.R. Part 20. This information is submitted to the U.S. Food and Drug Administration for purposes of regulatory review in connection with a Modified Risk Tobacco Product application and may be disclosed only to the extent permitted by applicable law.