



MODIFIED RISK GRANTED ORDERS– EXPOSURE MODIFICATION

22nd Century Group Inc.
Attention: Karen E. Delaney, Program Manager
8560 Main Street, Suite 4
Williamsville, NY 14221

FDA Submission Tracking Numbers (STNs): MR0000159-MR0000160, see Appendix A

Dear Karen Delaney:

We completed review of your MRTPAs¹ and are issuing modified risk granted orders for the tobacco products identified in Appendix A.

Based on our review of your MRTPAs, we determined that the proposed modified risk tobacco products, as described in your applications and specified in Appendix A, have 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. We authorize marketing of the tobacco products as modified risk tobacco products with reduced exposure claims, including²:

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

Where any of the reduced exposure claims listed in Appendix A are used in the product label, labeling, or advertising (LLA), under section 911(h)(1) and 911(h)(3)(B), this order requires that the LLA must also include the following condition of use: “Helps you smoke less.” Additionally, we recommend that the LLA include the disclaimer:³ “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.”

Under the provisions of section 911, you may introduce or deliver for introduction into interstate commerce the modified risk tobacco products, in accordance with this exposure modification order. Under section 911(g)(2)(C)(ii), this order is conditioned on your agreement to conduct postmarket surveillance and studies (PMSS) in accordance with a protocol approved by FDA and to submit the results of such PMSS annually. See Appendix B for information on required PMSS. This order also

¹ Modified Risk Tobacco Product Applications (MRTPAs) submitted under section 911(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

² See Appendix A for additional claims.

³ In your MRTPAs, you refer to the statement, “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.” variously as a “disclaimer” (Section V “Labels, Labeling, and Advertising,” p. 3; Section VII “Summary of All Research Findings,” p. 72) and “voluntary warning” (Section V “VLN™ Cigarettes: Labels, Labeling, and Advertising,” pp. 2, 8-9). In this order, the word “disclaimer” refers to your use of this term and does not reflect FDA’s independent conclusion regarding characterization of the information.

includes requests related to other record retention and reporting, as outlined in all attached appendices.

This order expires five years from the issue date of this letter. If you wish to renew your order, we recommend a request for renewal is received by FDA at least 360 days prior to the expiration date. Your renewal may cross-reference your MRTPAs that are subject to these orders.

The requirements in this exposure modification order are intended to help ensure that your modified risk tobacco products will continue to satisfy the requirements of section 911(g)(2)(A) and (B). However, compliance with these requirements alone is not a guarantee that the modified risk tobacco products will continue to be appropriate to promote public health and continue to be expected to benefit the health of the population as a whole, particularly if, despite these measures, there is a significant increase in youth initiation or initiation by non-users. FDA will continue to monitor the marketing of your products and their impact on the population.

This order authorizing the marketing of these modified risk tobacco products does not mean FDA “approved” the products specified in Appendix A; therefore, you may not make any express or implied statement or representation directed to consumers that conveys, misleads, or would mislead consumers into believing, among other things that the modified risk tobacco products specified in Appendix A, are “approved” by FDA (see Section 301(tt) of the FD&C Act). Moreover, because these products have not been authorized under section 911(g)(1) (risk modification order), you may not market these products with reduced risk claims.

The exposure modification order under 911(g)(2), that these modified risk tobacco products are subject to, is subject to withdrawal as described in section 911(j) of the FD&C Act.

We remind you that the modified risk tobacco products specified in Appendix A are subject to the requirements of the associated December 17, 2019 PMTA order and appendices, FD&C Act, and its implementing regulations, and Federal Cigarette Labeling and Advertising Act (15 U.S.C. 1333). It is your responsibility to ensure the tobacco products specified in Appendix A comply with all applicable statutory and regulatory requirements. FDA will monitor your compliance with all applicable statutes and regulations.

In accordance with 40 CFR 1506.6, we will make your Environmental Assessment (EA) publicly available.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal^{4,5} using eSubmitter.⁶ Alternatively, submissions may be mailed to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The CTP Portal and FDA's Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; if the upload is successful, submissions are considered received by DCC on the day of upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date⁷; if the due date falls on a weekend or holiday, the delivery must be received on or before the preceding business day. We are unable to accept regulatory submissions by e-mail.

If you have any questions, please contact Kristopher Van Amburg, Regulatory Health Project Manager, at (301) 348-3032 or Kristopher.VanAmburg@fda.hhs.gov.

If you have any questions regarding postmarket activities for the tobacco products subject of these orders, please contact Michael Gu, Acting Director, Division of Enforcement and Manufacturing, at CTP-OCE-Postmarket@fda.hhs.gov.

Sincerely,

/s/

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosures:

Appendix A – Tobacco Products Subject of This Letter
Appendix B – Postmarket Surveillance and Studies
Appendix C – Recordkeeping and Retention
Appendix D – Manufacturing Information

⁴ <https://www.fda.gov/tobacco-products/manufacturing/submit-documents-ctp-portal>

⁵ FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.

⁶ <https://www.fda.gov/industry/fda-esubmitter>

⁷ <https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/contact-ctp>

Appendix A⁸

8

Tobacco Products Subject of This Letter

Common Attributes of MRTPAs	
Submission date	May 17, 2019
Receipt date	May 20, 2019
Applicant	22nd Century Group Inc.
Product Manufacturer	NASCO Products LLC
Product Category	Cigarettes
Product Sub-Category	Combusted, Filtered
Product order under 911(g)	911(g)(2) Exposure Modification Order
Reduced Exposure Claims	<ul style="list-style-type: none"> • “95% less Nicotine • “Helps reduce your nicotine consumption” • “...greatly reduces your nicotine consumption” • “VLN™ cigarettes are substantially lower in nicotine content than any other cigarettes currently available to smokers in the United States. VLN™ cigarette contain an average of just 0.27 mg of nicotine.” • “Without exception, VLN™ cigarettes contain at least 95% less nicotine than the top 100 cigarette brands in the United States.” • “22nd Century's VLN™ cigarettes contain an average of 0.27 mg nicotine - -at least 95% less nicotine compared to conventional cigarettes.” • “22nd Century's VLN™ cigarettes feature the same nicotine content as the lowest nicotine style of the Company's SPECTRUM research cigarettes.” • “VLN™ cigarettes contain 0.27 ± 0.1 mg nicotine.” • “As a result of our unique technology and plant breeding expertise, VLN™ tobacco grows with 95% less nicotine than conventional tobacco.” • Graph depicting nicotine levels of VLN™ cigarettes compared to several other cigarette brands.
Attributes	Tobacco Product
MR0000159: VLN™ King	
Package type	Hard Pack
Package quantity	20 Cigarettes
Characterizing flavor	None
Length	83 mm
Diameter	7.9 mm
Ventilation	13 %
MR0000160: VLN™ Menthol King	
Package type	Hard Pack
Package quantity	20 Cigarettes
Characterizing flavor	Menthol
Length	83 mm
Diameter	7.9 mm
Ventilation	13 %

⁸ Brand/sub-brand or other commercial name used in commercial distribution.

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Appendix B

Postmarket Surveillance and Studies (PMSS)

Under Section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]."

I. PMSS Content

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco products, which are the subject of this order, continue to satisfy the requirements of section 911(g)(2)(A) and (B), is driven, in part, by use behavior.

Your proposed postmarketing surveillance and studies (PMSS) include a 6-month cross sectional study (n=1,000) to assess product knowledge, use, and attitudes among people who started smoking VLN™ cigarettes within the past 6 months (Section X "Postmarket Surveillance Program," pp. 5-6). Primary objectives of the study would be to assess VLN™ product knowledge, use patterns, and demographic characteristics of VLN™ smokers (age, gender, ethnicity, three-digit zip code). Secondary objectives would be to assess the use of other tobacco products at the time of initiation of VLN™ cigarettes, describe how users learned about VLN™ cigarettes, and describe personal factors motivating initiation of VLN™ cigarette use. You also propose to recruit a subset of the cross-sectional study participants into a longitudinal study that would evaluate reductions in cigarette use among VLN™ smokers prospectively over a 12-month period. We agree with the constructs you propose to assess in your 6-month cross-sectional study (e.g., knowledge of VLN™'s product features – including understanding of the health risks associated with various patterns of use – as well as demographic characteristics and current, previous, and subsequent use patterns with VLN™ and other cigarettes). In your longitudinal study, monitoring use of the products that are the subject of this order in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new MRTP users were never, former, or current smokers, or other tobacco product users before initiating the MRTPs and the extent to which new users of the MRTPs become exclusive VLN™ cigarette users, dual users with combusted cigarettes or other tobacco products, or transition to normal nicotine content (NNC) cigarette smoking over time. These studies must be designed to observe behavior over a sufficient period of time to examine, for instance, the extent to which dual use of VLN™ cigarettes and combusted cigarettes is a transitional versus stable pattern of use.

Your studies must also include an assessment of consumers' understanding of the modified risk claims and perceptions of the products. In particular, PMSS must assess the extent to which users of these products understand that VLN™ cigarettes are just as toxic as other cigarettes when used in the same way (i.e., with the same frequency and for the same duration). Additionally, you must assess the extent to which VLN™ cigarette users understand that to get long-term benefits, they have to use VLN™ cigarettes to substantially reduce the amount of cigarettes that they smoke. Thus, you must assess whether current smokers who take up VLN™ understand that they should cut down on their overall cigarette smoking and that replacing their other cigarettes with VLN™ without substantially cutting down is not sufficient to yield long-term benefits.

Your studies must have clear research objectives, including assessing whether the MRTPs are leading to changes in product use behaviors that are expected to benefit population health. Your protocol must include a statistical analysis plan describing, among other things, how you plan to conduct inferential statistical analyses to address these objectives.

Your PMSS must also include a postmarket study testing the effects of the disclaimer¹⁰ (“Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.”) on consumer understanding of VLN™ cigarettes’ health risks and conditions of use. The disclaimer has several features that are inconsistent with expert recommendations for designing disclaimers, and poorly designed disclaimers have the potential to confuse consumers and change their perceptions, attitudes, or decisions in a manner opposite of that intended (Green & Armstrong, 2012). Conducting a postmarket study to test the disclaimer can provide FDA with evidence about whether the disclaimer helps enable consumers to understand that VLN™ cigarettes present the same disease risks as other cigarettes if smoked in the same way, or if it worsens existing misperceptions about the health risks of cigarettes containing reduced nicotine levels. If FDA determines that the disclaimer causes such misperceptions, then FDA will require that you remove the disclaimer from the modified risk labels, labeling and advertising and any advertising where it is included.

FDA also recommends that, if you seek to use any modified risk ads that are potentially youth-appealing, then you should conduct consumer testing of the ads to determine whether they would increase the likelihood of use among nonsmokers, particularly minors (under age 21). For example, FDA found that some of the original advertising submitted with these applications contained potentially youth appealing imagery. Although you subsequently withdrew it from the MRTPAs, this is an example of advertising that FDA has concerns about and we suggest that if you seek to use ads that are potentially youth appealing, then you first study them to determine the effect on initiation by non-users, particularly youth; imagery and themes known to resonate with youth include aspirational content depicting tobacco use as “cool,” attractive, rebellious, or risky, or as a means to make one more popular, desirable, or independent (U.S. Department of Health and Human Services, 2012).

In addition, FDA has determined that assessing the impact of your MRTP orders on uptake of the products requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by product, major metropolitan areas, and channels where the products are sold (e.g., convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the tobacco products by quarter since the date of issuance of your modified risk granted orders (for the initial reporting period) or the previous reporting period (for all reports that follow), including, for each MRTPA STN, total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were distributed and sold during the reporting period (e.g., convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops).
- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly

¹⁰ In your MRTPAs, you refer to the statement, “Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.” variously as a “disclaimer” (Section V “Labels, Labeling, and Advertising,” p. 3; Section VII “Summary of All Research Findings,” p. 72) and “voluntary warning” (Section V “VLN™ Cigarettes: Labels, Labeling, and Advertising,” pp. 2, 8-9). In this order, the word “disclaimer” refers to your use of this term and does not reflect FDA’s independent conclusion regarding characterization of the information.

growth rate (percent change) in total U.S. sales and distribution of the tobacco products for each MRTPA STN, post-MRTP authorization.

MRTP Use and Health Risk – Serious and Unexpected Adverse Experiences

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be 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 (section 911(g)(2)(A-B)), your PMSS must include ongoing surveillance of all adverse experiences including those that are both serious and unexpected associated with the use of the MRTPs. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience; or tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported serious and reported unexpected adverse experiences for the tobacco products, which includes a listing of all serious and unexpected adverse experiences during the reporting period and a cumulative list including all serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.

In addition, the PMTA order for your tobacco products, issued on December 17, 2019, requires you to report to the FDA all adverse experiences that are serious, whether expected or unexpected, and your analysis of the association between the adverse experience and the tobacco product within 15 calendar days after the report is received by you. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for these products. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS ADVERSE EXPERIENCE REPORT FOR STNs PM0000491-PM0000492 and MR0000159-MR0000160.**

For purposes of this reporting, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;
- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

Surveillance of New Research Study Findings on the MRTPs and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTPs and consumer perceptions, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing previously unreported (new) findings both in published or unpublished studies conducted by you or on your behalf and in published or otherwise available studies regarding the MRTPs and consumer perceptions, behavior, or health. Your annual PMSS report must include:

- A summary of significant findings about the tobacco products from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this order.
- A summary of significant findings in publications not previously reported and full copies of the articles. These must include any new scientific data (published or otherwise) on the MRTPs and consumer perception, behavior, or health.

Modeling the Impact of the MRTP on Population Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include computational modeling of the impact of the MRTPs on population health. Such modeling must incorporate data and information collected through PMSS, including the percentage of former smokers who start using VLN™ cigarettes; the percentage of current smokers who start using VLN™ cigarettes and become dual users; the percentage of current smokers who switch completely to VLN™ cigarettes; the percentage of youth and young adults under the federal minimum age of sale who start using VLN™ cigarettes; and the percentage of individuals who start using VLN™ cigarettes and then initiate or re-initiate NNC combusted cigarettes. Postmarket modeling must also incorporate the latest information on acute and long-term health effects of using the proposed MRTPs relative to NNC combusted cigarette smoking in order to assess the short and long-term population health impacts of the marketing. Your annual PMSS report must include:

- A description of the methodological approach used in the model;
- A copy of the model or its underlying code, such that FDA can independently run and verify the model inputs and outputs;
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information; and
- A summary of the modeling results and their implications for assessing whether the MRTPs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole.

II. Submitting PMSS Protocols and Reports

As required under section 911(g)(2)(C)(ii) of the FD&C Act, your modified risk order is conditioned on your agreement to conduct PMSS under an approved protocol, and to submit the results for FDA to determine the impact of the order and review the accuracy of determinations on which the order is based. Within 30 days of receiving this notice, you must submit your agreement to conduct PMSS and complete protocols for your PMSS. Label your submission clearly as a “PMSS Protocol” and reference your MRTPA Submission Tracking Numbers (STNs). If you have more than one protocol, each protocol should be a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study. Within 60 days of receipt of the protocol(s), FDA intends to review the protocol(s) and evaluate if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of data or other information that has the potential to enable FDA to accurately determine the impact of the order on consumer perception, behavior and health and to review the accuracy of the determinations upon which the order was based, pursuant to section 911(g)(2)(C)(ii) of the FD&C Act. FDA will notify you of, and provide opportunities to address, any deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per the timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis, and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(g)(2)(C)(iii) requires that the results of the PMSS be submitted on an annual basis. These reports must be identified as “PMSS Report” and the MRTPA STNs should be referenced for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable, the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the approved timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.

Appendix C

Recordkeeping and Retention

The exposure modification order for your modified risk tobacco products is effective for five years from the issue date of the order. If you wish to renew your order, we recommend you submit a request for renewal 360 days prior to the end of your effective timeframe. In order to help ensure that your exposure modification order meets the standard for renewal and to help expedite the review of any renewal applications, we request that you establish and maintain the records listed below. The records should be retained for a period of not less than four years from the date of distribution of the last batch of the tobacco products listed in your orders under section 911(g)(2). The records should be legible, written in English, and available for inspection and copying by officers or employees duly designated by the Secretary upon request. Please note that Appendix B requires you to periodically submit some of these records to FDA (e.g., in PMSS reports). Additionally, we remind you that the PMTA order for your tobacco products issued on December 17, 2019, also requires you to establish and maintain records, some of which overlap with the records listed below:

- The MRTPAs submitted prior to the orders
- Postmarket reports, as described in Appendix B, and adverse experience reports, including all relevant documentation associated with the experience
- Records of all nonclinical or clinical studies, including:
 - Source data;
 - Study protocols (including statistical analysis plan);
 - Amendments showing the dates and reasons for any protocol revisions;
 - Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals or non-approvals;
 - Informed consent forms;
 - Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC;
 - Investigator financial disclosure statements;
 - Progress reports;
 - Monitoring reports;
 - Adverse experience reports;
 - Case report forms/subject diaries/medical records/laboratory reports;
 - Subject data line listings/observation records;
 - Test article accountability records;
 - Study results/protocol summaries/study reports; and
 - Certifications and amendments to certifications
- Records pertaining to the manufacture, in process and release testing, production process (including any changes to the process, facility, or controls), packaging, storage, and stability monitoring and testing (including protocol and results) of the products
- Records pertaining to the sale, distribution, or other disposition of the products, specifically:
 - A list of distributors and retailers of the products, including brick-and-mortar and digital. For the purposes of this order, here and throughout the document, “digital” includes internet/online and mobile;
 - Any available information (not to include personally identifiable information) about product purchases, such as purchasers’ demographics (e.g., age, gender, race/ethnicity, geographic region) and previous or current use of other tobacco products (i.e., dual use);
 - With respect to individuals under the federal minimum age of sale of tobacco products, policies and procedures regarding restrictions on access to the products, including purchaser age and identity verification processes

- Records pertaining to the products' labeling, advertising, marketing, and/or promotion – whether conducted by you, on your behalf, or at your direction – including:
 - Specimens of all labeling (including all labeling variations, such as those reflecting different required warnings), labels, inserts/onserts, instructions, and other accompanying information;
 - Copies of all advertising, marketing, and/or promotional materials published, disseminated to consumers, or for use in engaging or communicating with consumers;
 - Copies of any formative research studies conducted among any audiences in the formation of the labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
 - Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
 - Copies of any contractual agreements regarding the creation and/or dissemination of the products' labeling, advertising, marketing, and/or promotional materials, including for example, in print media, online or through digital platforms (e.g., social media and mobile applications), such as influencers, bloggers, and ambassadors, on your behalf, or at your direction;
 - Copies of all advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including any:
 - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;
 - Targeting of specific adult audiences by age-range(s), including young adults, ages 21-24, and other demographic and/or psychographic characteristics that reflect your intended target audience;
 - With respect to individuals under the federal minimum age of sale of tobacco products, actions taken to restrict access to the product and limit exposure to the products' labeling, advertising, marketing, and/or promotion;
 - Use of owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the product;
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 - Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the product;
 - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated and how access will be restricted to individuals at or above the federal minimum age of sale of tobacco products; or
 - Use of public-relations or other communications outreach to create labeling for, advertise, market, and/or promote the products;
 - Copies of all records pertaining to the actual delivery of advertising impressions, including media tracking and optimization, by channel, by product (if applicable), by program (where applicable), and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), media buy summaries, program lists, number of units by program, percent audience compositions by age breakouts (i.e., 21+, 2-11, 12-17, 18-24, 25-54, 55+) by program,

- audience indices by age breakouts (i.e., 2-11, 12-17, 18-24, 25-54, 55+) by program, reach and frequency, any other parameters purchased against the buying demographics, and all post-launch delivery-verification reports for other paid media submitted to you or entities working on your behalf or at your direction from an accredited source; and
- Policies and procedures for real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products, including documentation of such monitoring activities and implementation of corrective and preventive measures
 - Health hazard analyses, if performed voluntarily or directed by FDA
 - Records pertaining to any and all complaints associated with any of the products that you receive or of which you are aware; such records may also include your analysis of those complaints

Appendix D

Manufacturing Information

The PMTA order for your tobacco products, issued on December 17, 2019, requires you to report to the FDA manufacturing information. We request that when submitting such reports, you reference both your PMTA and your MRTPA for the product. When cross-referencing, please provide the date of submission and location in the submission where the information is covered.

For each twelve-month reporting period, the annual reports should include:

- A cover letter that includes the following text in your subject line: **ANNUAL REPORT for PM0000491-PM0000492 and MR0000159-MR0000160**. The cover letter should include the STN(s), static product ID if applicable, and corresponding tobacco product name(s), firm name, date of report, reporting period.
- A description of each change made to the manufacturing process, facilities, or controls during the reporting period including:
 - A comparison of each change to what was described in the PMTA/MRTPA;
 - The rationale for making each change; and
 - A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of the tobacco products and the basis for concluding that each manufacturing change did not result in any modification to the products.¹¹
- A summary of all manufacturing deviations, investigations, and corrective and preventive actions, including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding, and distribution and indicate any deviation(s) that may affect the characteristics of the products. For additional information on manufacturing deviations, see below.

Manufacturing Deviations

You should promptly investigate all manufacturing deviations including, but not limited to, those associated with processing, testing, packing, labeling, storage, holding, and distribution. The PMTA order for your tobacco product, issued on December 17, 2019, requires that, for products that have been distributed, if a deviation occurs that you determine presents a reasonable probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in tobacco products on the market that would cause serious, adverse health consequences or death you are required to report the deviation to FDA within 15 calendar days of identification. We request that when submitting such reports, you reference both your PMTA and your MRTPA for the product.

Discontinuation and Reintroduction

If you discontinue the manufacture, preparation, compounding, or processing for commercial distribution of the modified risk tobacco product and later decide to reintroduce the modified risk tobacco product into the market, please contact the Office of Compliance and Enforcement prior to reintroduction. Section 905(i)(3) of the FD&C Act requires you to update your product listing biannually to reflect any products that have been discontinued and/or reintroduced into interstate commerce.

¹¹ We note that any modifications made to a tobacco product that render it a new tobacco product are subject to the premarket review requirements under section 910 of the FD&C Act.