5.: APPENDIX CONTENT AND FILE LISTING: ENVIRONMENTAL ASSESSMENTS

5. APPENDIX CONTENT AND FILE LISTING: ENVIRONMENTAL ASSESSMENTS

Table 5-1: Appendix Content and File Listing[1]

File Listing	File Format
Appendix 5-1-1 – Environmental Assessment Report for VERVE Chews Blue Mint	PDF
Appendix 5-1-2 – Environmental Assessment Data Summary for VERVE Chews Blue Mint	PDF
Appendix 5-1-3 – Environmental Assessment FDA Citations for VERVE Chews Blue Mint	PDF
Appendix 5-2-1 – Environmental Assessment Report for VERVE Chews Green Mint	PDF
Appendix 5-2-2 – Environmental Assessment Data Summary for VERVE Chews Green Mint	PDF
Appendix 5-2-3 – Environmental Assessment FDA Citations for VERVE Chews Green Mint	PDF
Appendix 5-3-1 – Environmental Assessment Report for VERVE Discs Blue Mint	PDF
Appendix 5-3-2 – Environmental Assessment Data Summary for VERVE Discs Blue Mint	PDF
Appendix 5-3-3 – Environmental Assessment FDA Citations for VERVE Discs Blue Mint	PDF
Appendix 5-4-1 – Environmental Assessment Report for VERVE Discs Green Mint	PDF
Appendix 5-4-2 – Environmental Assessment Data Summary for VERVE Discs Green Mint	PDF
Appendix 5-4-3 – Environmental Assessment FDA Citations for VERVE Discs Green Mint	PDF
Ingredient 1 through Ingredient 78	78 PDFs

[1] VERVE® is a registered trademark; however the ® symbol intentionally does not appear in the file names or in the document descriptions provided by the vendors to avoid the use of special characters.

(b) (4)

ENVIRONMENTAL ASSESSMENT
TRADE SECRET/CONFIDENTIAL COMMERCIAL INFORMATION
FOR THE PRODUCT IDENTIFIED AS VERVE® CHEWS BLUE MINT

Memorandum

To:	Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC
From:	(b) (4)
Date:	May 24, 2018
Subject:	Environmental Assessment for the Premarket Tobacco Product Application for the Product Identified as VERVE® Chews Blue Mint

This environmental assessment was prepared in accordance with 21 CFR 25.40, the Food and Drug Administration's (FDA's or Agency's) regulation implementing the National Environmental Policy Act of 1969. Under NEPA, "all applications or petitions requesting Agency action require the submission of an environmental assessment or a claim of categorical exclusion."[1]

(b) (4) respectfully submits the following environmental assessment in support of the *Premarket Tobacco Product Application (PMTA)* for the product identified as *VERVE® Chews Blue Mint* (referred to throughout this assessment as the "New Product") pursuant to 21 CFR 25.20 because there is no applicable categorical exclusion for this type of application.

This environmental assessment was conducted in accordance with 21 CFR 25.40 and relevant aspects of FDA technical guidance documents including:

- *Environmental Considerations for Tobacco Product Applications Submitted to CTP, presented by Cristi Stark, M.S., Associate Director for Science Policy, Office of Science, CTP, FDA (August 2016);*
- *Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I (March 2001); and*
- *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).*

[1] 21 CFR 25.15(a)

This environmental assessment was prepared at the direction of Altria Client Services LLC (ALCS) on behalf of U.S. Smokeless Tobacco Company LLC (USSTC), a wholly owned subsidiary of Altria Group Inc. The potential aquatic, atmospheric, and terrestrial environmental impacts of FDA's approval of the PMTA and subsequent marketing of the New Product were considered using a conservative set of assumptions. The assessment identified no significant environmental risks, and a Finding of No Significant Impact by FDA is warranted for the environmental assessment of the New Product.

This memorandum contains trade secret and confidential commercial information that USSTC considers to be proprietary and highly sensitive, and which is protected from disclosure under the Food, Drug and Cosmetic Act §§ 301(j) and 906(c) (21 U.S.C. §§ 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. § 1905), the Freedom of Information Act (5 U.S.C. § 552), and FDA's implementing regulations, 21 CFR Part 20. If FDA receives a request for these records and tentatively determines that any portion of this submission is disclosable, USSTC requests that FDA provide notice and opportunity for USSTC to object to any disclosure in accordance with 21 CFR § 20.47 and 21 CFR § 20.61. USSTC reserves all of its legal rights to protect against public disclosure of its trade secret and confidential commercial information and to seek legal recourse against anyone who discloses such information without legal authorization.

1. DATE

May 24, 2018

2. NAME OF APPLICANT/SUBMITTER

Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC

3. ADDRESS

2325 Bells Road, Richmond, Virginia 23234

4. MANUFACTURER

U. S. Smokeless Tobacco Company LLC

5. DESCRIPTION OF PROPOSED ACTION

The proposed action is for FDA to issue a market authorization order under Section 910(c)(1)(A)(i) of the Food, Drug and Cosmetic Act (FD&C Act)[2] to introduce the New Product into interstate commerce. Through a PMTA for the New Product, USSTC is requesting approval from FDA to introduce the New Product into interstate commerce for commercial distribution in the United States. USSTC is including this environmental assessment with its submittal of the PMTA to FDA for the New Product.

6. IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

6.1. Type of Tobacco Product

Verve® chews are a chewable, non-dissolvable, tobacco-derived nicotine product (known as an oral nicotine-delivery product). The chewable form of the New Product has a soft, flexible texture.

6.2. Estimated Market Volumes

The following table presents the estimated first-year and fifth-year market volumes for the New Product. These estimated market volumes form the basis for the environmental exposure estimates provided in this assessment.

Table 1 – Estimated First-Year and Fifth-Year Market Volumes for the New Product

Name	Unit	New Product	
		First-Year Projected Market Volume	Fifth-Year Projected Market Volume
VERVE® Chews Blue Mint	Tubes[3]	(b) (4)	
	Metric Tons		

6.3. Product Composition

The New Product contains tobacco-derived nicotine, (b) (4), non-tobacco cellulose fiber, flavorings, texture modifiers, binders and colorants.

[2] 21 U.S.C. 387j

[3] There are 12 chews in one tube.

6.3.1. *Product*

The formulation of the New Product is given in the following table. All values are reported in milligrams (mg).

Table 2 – Product Formulation

ID #[4]	CAS Number	Substance	Amount per Piece (mg)
1			(b) (4)
2			
3			
4			
5			
7			
8			
9			
11			
12			
13			
14			
16			
17			
18			
19			

[4] The ID# is a unique number for each ingredient; it corresponds to the list of ingredients in Confidential Appendix 5-1-2.

Table 2 – Product Formulation

ID #[1]	CAS Number	Substance	Amount per Piece (mg)
20			(b) (4)
21			
24			
25			
26			
27			
28			
29			
30			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			

Table 2 – Product Formulation

ID #[1]	CAS Number	Substance	Amount per Piece (mg)
43			(b) (4)
44			
46			
47			
49			
50			
54			
55			
56			
57			
59			
60			
61			
62			
63			
64			
65			
67			
69			
71			

Table 2 – Product Formulation

ID #[4]	CAS Number	Substance	Amount per Piece (mg)
72			(b) (4)
73			
74			
75			
76			
78			

6.3.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

6.3.2. Packaging

Packaging material for the New Product comprises the following components, with weight represented on a per product basis. The individual chews (12) are packaged in a Tube which contains a tube, button (lid), label and a shrink band. USSTC has designed all packaging materials to meet FDA's standard for direct and indirect food additives set forth in Title 21 of the Code of Federal Regulations (CFR).

Table 3 – Characterization and Weight of Packaging Materials[5]

Packaging Component	Package Composition	Weight (grams)
Tube		(b) (4)
Button		
Label		

[5] There are 12 chews per tube, 5 tubes per carton and 5 cartons per case.

Table 3 – Characterization and Weight of Packaging Materials[5]

Packaging Component	Package Composition	Weight (grams)
Tamper Evident Shrink Band	(b) (4)	
Carton		
Carton Shrink Film		
Case		

6.4. Location of Manufacture

The New Product will be manufactured at U.S. Smokeless Tobacco Products LLC, located at (b) (4) . U.S. Smokeless Tobacco Products LLC is a business entity of United States Smokeless Tobacco Company (USSTC). The (b) (4) for the New Product.

6.5. Location of Use

USSTC intends to market the New Product to adult consumers throughout the United States.

6.6. Disposal Sites

The distribution of waste generated due to disposal of the New Product and/or packaging is expected to correspond to the pattern of product use. Disposed materials will either enter the recycling stream or be disposed of in municipal solid waste (MSW) landfills or as litter. Additional information is provided in Section 7.1.3 below.

7. ENVIRONMENTAL ISSUES

7.1. Introduction of the Product into the Environment

7.1.1. As a Result of Manufacture

No significant environmental impacts are anticipated as a result of manufacturing the New Product. (b) (4)

(b) (4)

According to the U.S. Environmental Protection Agency (USEPA)'s most recent National Biennial Report data (https://rcrainfo.epa.gov/rcrainfoweb/action/modules/br/summary/view), 33,646,921 tons of hazardous wastes were generated across the United States in 2015. Of this amount, over 2,688,613 tons were incinerated or used (combusted) for energy recovery. Assuming the entire production volume is disposed of by the manufacturing facility, the New Product

is expected to generate up to (b) (4) of hazardous waste per year.[6] This represents up to (b) (4) of the total hazardous waste in the country and up to (b) (4) of the total hazardous waste treated by incineration or used (combusted) for energy recovery in the country. Thus, the contribution of the New Product to total hazardous waste generated and treated by incineration (or energy recovery) annually in the United States is miniscule. Therefore, additional resources (e.g., new incineration or similar treatment facilities, etc.) will not be required for disposal of the New Product.

Section 7.1.3 addresses the solid waste generation expected to result from use of the New Product. The New Product following use by consumers is an exempt household hazardous waste and is not subject to regulation as hazardous waste.

No significant environmental impacts are anticipated as a result of manufacturing the New Product.

7.1.2. As a Result of Use

The aquatic environment is the primary compartment of concern for environmental releases resulting from use of the New Product. The New Product is used orally. Therefore, exposure to the terrestrial and atmospheric environments is not anticipated.

7.1.2.1. Aquatic

7.1.2.1.1. Product

The New Product ingredients are expected to be released primarily to the aquatic environment via excretion as a result of product use. To quantify the anticipated amount of each chemical substance contained in the New Product to the aquatic environment, (b) (4) calculated the annual load (kilograms per year, or kg/yr) and the aquatic expected introduction concentration (EIC) (micrograms per liter, or µg/L). (b) (4) applied the approach FDA established for human drugs and biologics to calculate the aquatic EIC as follows:

[6] Maximum US tons of MSW per year = A*B*C; where A = Maximum Annual Shipping Quantity between 1st Year and 5th Year (g), B = Weight of product (g), C = 1 / 907,185 g/US Ton (Conversion from g to US Tons)

EIC-aquatic (ppb or µg/L) =A * B * C * D, where

A=kg/yr produced,

B=1/1.071x10^{11} L/day entering POTW (Publicly Owned Treatment Works facility)

(Source: Clean Watersheds Needs Survey (NWNS) 2012 Data and Reports, Detailed Listing of Waste Water Treatment Plant Flows for the Nation accessible at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:4:::::RP::),

C=year/365,

D=10^{9} µg/kg

In calculating the aquatic EIC values, (b) (4) maintained the following conservative assumptions that were established in FDA guidance:[7]

- The kg/year produced is based on the highest quantity expected to be produced for direct use in any of the next five years;
- All product produced in a year is used and enters the POTW system [The ingredients are absorbed by the human body during use and 100% of the ingredients are then excreted to sanitary sewer and to treatment within the POTW];[8]
- New Product usage occurs throughout the United States in proportion to the population and amount of wastewater generated;
- No dilution occurs in receiving waters; and
- There is no metabolism.

The results of these calculations were compared to FDA's established concentration of concern (1 µg/L or ppb). As described in its 2001 technical guidance document, *Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I*, FDA considers this value to be below the level shown to have adverse effects in aquatic ecotoxicity studies with human drugs. This was deemed appropriate for the current assessment as No Observed Effect Concentration (NOEC) values for each substance, where available, are greater than 1 µg/L or ppb.

A brief summary of publicly available fate and effects data for each ingredient of the New Product is provided in Confidential Appendix 5-1-2 for reference.

[7] Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)

[8] (b) (4)

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
		(b) (4)

[9] (annual production forecast) x (relative amount in formulation)

[10] EI C-aquatic (ppb or µg/L)=A*B*C*D; where A=kg/yr produced, B=1/1.071x10[11] L/day entering POTW (Source: Clean Watersheds Needs Survey (NWNS) 2012 Data and Reports, Detailed Listing of Waste Water Treatment Plant Flows for the Nation accessible at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:4:::RP::), C=year/365, D=10[9] µg/kg

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
		(b) (4)

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
[redacted]		

(b) (4)

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
(b) (4)		

(b) (4) noted that in every case, the aquatic EIC is (b) (4) at the point of entry into the aquatic environment, which is below the relevant concentration of concern identified in FDA guidance.

7.1.2.1.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

In Table 4, (b) (4) noted that the EIC calculated for nicotine is (b) (4) at the point of entry into the aquatic environment and therefore below FDA's established concentration of concern. Nonetheless, fate and effects data for nicotine are discussed in detail in Sections 7.2 and 7.3 of this assessment.

7.1.2.1.2. Packaging

Packaging is not intended or expected to release chemical substances during use. Releases as a result of disposal are discussed in Section 7.1.3 of this assessment.

7.1.3. As a Result of Disposal

Following use by consumers, the New Product is an exempt household waste and is not subject to regulation as hazardous waste. The New Product will be disposed of in MSW landfills or as litter. The associated packaging materials will either be recycled or be disposed of in MSW landfills or as litter. The New Product will be disposed of in the same

way as other commercially marketed consumer chewable products (e.g., chewing gums or chewable tablets). The distribution of waste generated due to disposal of the New Product and packaging is expected to correspond to the pattern of product use throughout the United States.

Disposal following use of the New Product is not expected to require additional resources for waste disposal. The terrestrial environment is the primary compartment of concern for environmental releases of the New Product as a result of disposal. Any release to the aquatic environment as a result of disposal is addressed by the calculations conducted in Section 7.1.2.

7.1.3.1. Disposal of the Product Following Use

According to the U.S. Environmental Protection Agency (USEPA) document, *Advancing Sustainable Materials Management: 2014 Fact Sheet Assessing Trends in Material Generation, Recycling, Composting, Combustion with Energy Recovery and Landfilling in the United States*, 258 million tons of MSW were generated across the United States in 2014. Of this, over 89 million tons (34.6%) were recycled and composted, more than 136 million tons (52.6%) were discarded in a landfill, and more than 33 million tons (12.8%) were combusted with energy recovery (USEPA, 2016a). Chewable nicotine products (oral nicotine-delivery products) are not expected to be recycled.

Assuming the entire production volume is disposed of in a landfill, the New Product is expected to generate up to (b) (4) of MSW per year.[11] This represents up to (b) (4) of the total MSW in the country and up to (b) (4) of MSW that is disposed of in landfills in the country. Thus, the contribution of the New Product to total MSW disposed annually in the United States is miniscule. Therefore, additional resources (e.g., new landfills, recycling centers, etc.) will not be required for disposal following use of the New Product.

Proper disposal will be to landfill and not directly to the terrestrial environment. Disposal to MSW landfills will not result in adverse effects to the environment based on landfill design and regulatory requirements. Disposed waste streams within a landfill are prevented from entering the environment and ultimately landfill leachate is treated and/or sent to POTWs for effective treatment.

Disposal following use of the New Product is not expected to result in new or additional compounds emitted to the environment. USSTC anticipates the New Product will be

[11] Maximum US tons of MSW per year = A*B*C; where A = Maximum Annual Shipping Quantity between 1st Year and 5th Year (g), B = Weight of product (g), C = 1 / 907,185 g/US Ton (Conversion from g to US Tons)

disposed of following use in the same way as other commercially marketed consumer chewable products (e.g., chewing gums or chewable tablets). The distribution of waste generated due to disposal of the New Product is expected to correspond to the same pattern of product use. No new or additional environmental effects, as defined within 40 CFR 1508.8, are anticipated. However, improper disposal may occur. The calculations provided in Section 7.1.3.2 conservatively address product that is inappropriately disposed of directly to the environment.

7.1.3.2. Terrestrial

7.1.3.2.1. Product

Introduction of the New Product to the terrestrial environment was calculated as surface density. Absent guidance from FDA on the appropriate duration to be used for this calculation and because it is conservatively assumed there is no metabolism or depletion in the environment, a timeframe had to be selected. Therefore, the terrestrial surface density of each ingredient was calculated on a per day basis.

The daily terrestrial surface density values are presented in following table as the production tonnage distributed across the surface area of the United States per day (nanograms per square meter per day, or ng/m^2 per day). These values were based on the very conservative assumptions that the entire production volume was introduced to commerce and that the New Product is released to the terrestrial environment in its complete and unused state. The calculation is shown in the footnote for the table.

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)[12]
(b) (4)	

[12] Daily Surface Density (ng/m^2 per day) = A*B*C*D*E; where A = mg/yr produced, B = 1/9.158x10^6 km^2 surface area of the United States, C = year/365 days, D = 10^6 km^2/m^2, E = 10^6 ng/mg

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)
[redacted]	(b) (4)

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)[1]
(b) (4)	

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)[1]
(b) (4)	

The daily terrestrial surface density values presented as a production tonnage distributed across the surface area of the United States are (b) (4) ng/m^2 per day as determined using

the calculations shown in the footnote in the table above. The values are so small that exposure to the New Product in the terrestrial environment as described here would not have a significant effect.

Based on the mass of non-nicotine ingredients shown in Table 2 and publicly available environmental fate and effects data, a single used or unused chew that is improperly disposed is not expected to cause localized effects to the terrestrial environment. Adverse effects are highly unlikely because improper disposal of chews should occur only on rare occasions and the non-nicotine ingredients are expected to exhibit a low order of environmental toxicity.

7.1.3.2.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

The daily terrestrial surface density value for nicotine as the production tonnage distributed across the surface area of the United States per day (ng/m^2 per day)[13] is (b) (4) ng/m^2 per day. This was based on the very conservative assumptions that the entire production volume was introduced to commerce and that the New Product is released to the terrestrial environment in its complete and unused state.

(b) (4)

[13] Daily Surface Density (ng/m^2 per day) = A*B*C*D*E; where A = mg/yr produced, B = 1/9.158x10^6 km^2 surface area of the United States, C = year/365, D = 10^{-6} km^2/m^2, E = 10^6 ng/mg

7.1.3.3. Disposal of Packaging Following Use

The New Product's packaging is expected to be disposed of following use in the same way as packaging from other commercially marketed consumer chewable products. The distribution of waste generated due to disposal of packaging is expected to correspond to the same pattern of product use.

According to the USEPA document, *Advancing Sustainable Materials Management: 2014 Fact Sheet Assessing Trends in Material Generation, Recycling, Composting, Combustion with Energy Recovery and Landfilling in the United States,* 258 million tons of MSW were generated across the United States in 2014. Of this, over 89 million tons (34.6%) were recycled and composted, more than 136 million tons (52.6%) were discarded in a landfill, and more than 33 million tons (12.8%) were combusted with energy recovery (USEPA, 2016a). Assuming all of the New Product packaging is disposed of to landfill, packaging from the New Product is expected to generate up to (b) (4) of MSW per year[14]. This represents up to (b) (4) of the total MSW in the country and up to (b) (4) of MSW that is disposed of in landfills in the country. Thus, the contribution of the New Product's packaging to total MSW disposed annually in the United States is miniscule. Therefore, disposal of the New Product's packaging following use of the New Product is not expected to require additional resources (e.g., new landfills, recycling centers, etc.) for waste disposal.

Disposal of packaging following use of the New Product is not expected to result in new or additional compounds emitted to the environment. The materials used in the packaging of the New Product (b) (4) (b) (4) are common packaging materials used for consumer products in general. Proper disposal will be to landfill and not directly to the terrestrial environment. Disposal to MSW landfills will not result in adverse effects to the environment based on landfill design and regulatory requirements. The same or similar compounds and types of emissions are anticipated from disposal of the packaging of the New Product as those associated with disposal of the packaging of other consumer chewable products or consumer products in general. Thus, no new or additional environmental effects, as defined within 40 CFR 1508.8, are anticipated.

[14] (b) (4)

7.2. Fate of Product Released into the Environment

Due to its ecotoxicological relevance, we discuss the fate of nicotine released into the environment in this Section even though nicotine is below concentrations of concern based on the exposure assessments within this environmental assessment.

7.2.1. Nicotine

Quantitative Structure Activity Relationships (QSARs) have been used to describe the physical-chemical properties of nicotine and to provide predicted aquatic toxicity values to support the use of nicotine as a marker compound. Acceptable QSARs are not available to predict toxicity to terrestrial organisms. All QSAR predictions were determined using the USEPA's EpiWeb 4.1.[15]

7.2.1.1. Physical Chemical Properties

The physical-chemical properties of pure nicotine (CAS 54-11-5) and its metabolites are presented in the following table. Nicotine's physical-chemical properties can be used to assess the fate of nicotine introduced into the environment.

Nicotine introduced into water will stay mainly in water and will not readily partition to air based on its low Henry's Law Constant ($3x10^{-9}$ atmospheres – cubic meters per mole or atm-m^3/mole) and negative air/water partitioning coefficient (K_{aw} = -6.910) (USEPA, 2016b). Nicotine in water should not bioaccumulate or bioconcentrate in aquatic organisms (measured log K_{ow} = 1.17) (Hansch, Hoekman, Leo, Zhang, & Li, 1995). The predicted bioconcentration factor (log BCF) for nicotine of 0.440 supports this conclusion.

Nicotine introduced into the soil can volatilize to air based on the vapor pressure of 0.032 mm Hg (Boublik, 1984). However, the extent to which it actually volatilizes will depend on its sorption. The log K_{oc} predicted at neutral pH is 2.720 and indicates that nicotine in soil has moderate mobility. The mobility of nicotine, a weak acid (pK_a 8.5), is pH dependent and will increase at alkaline pH. Because nicotine is highly soluble (predicted solubility $1.000x10^6$ milligrams per liter, or mg/L) and has a negative K_{aw}, it will most likely partition to soil pore-water rather than air.

[15] The EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical/chemical property and environmental fate estimation programs developed by the USEPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). EPI Suite™ uses a single input to run the following estimation programs: KOWWIN™, AOPWIN™, HENRYWIN™, MPBPWIN™, BIOWIN™, BioHCwin, KOCWIN™, WSKOWWIN™, WATERNT™, BCFBAF™, HYDROWIN™, KOAWIN and AEROWIN™, and the fate models WVOLWIN™, STPWIN™ and LEV3EPI™. ECOSAR™, which estimates ecotoxicity, is also included in EPI Suite™ (USEPA, 2016b).

Table 6a – Predicted Physical-Chemical Properties of Nicotine and Related Compounds

CAS	IUPAC Name	Water Solubility	Vapour Pressure	Henry's Law Constant	Log K_{ow}	log K_{oc}	Log K_{oa}
		mg/L	mm Hg	atm-m^3/mol			
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	1 000E+06	3 200E-02	3 000E-09	9 980E-01	2 720E+00	8 080E+00
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	9 990E+05	3 810E-04	3 330E-12	3 400E-01	2 110E+00	8 038E+00
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	1 000E+06	2 160E-07	5 200E-13	-1 200E+00	1 010E+00	9 190E+00
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	1 000E+06	1 660E-05	1 520E-12	-3 000E-01	2 100E+00	9 900E+00
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	6 030E+05	5 120E-04	1 970E-10	3 210E-01	3 200E+00	8 480E+00
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	5 040E+03	5 130E-07	3 000E-14	6 860E-01	2 190E+00	1 260E+01
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	3 060E+05	6 040E-05	1 970E-10	5 970E-01	3 470E+00	8 690E+00
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	1 960E+05	6 680E-05	8 580E-11	8 120E-01	3 470E+00	8 850E+00

Table 6b – Predicted Physical-Chemical Properties of Nicotine and Related Compounds

CAS	IUPAC Name	Log K_{aw}	BCF	Photo-chemical half-life	Half-life in water	Half-life in soil
				hrs	days	days
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	-6.910E+00	4.400E-01	1.410E+00	3.750E+01	7.500E+01
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	-8.040E+00	5.000E-01	4.900E+00	3.750E+01	7.500E+01
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	-1.067E+01	5.000E-01	4.300E+00	3.750E+01	7.500E+01
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	-1.027E+01	5.000E-01	7.990E+00	6.000E+01	1.200E+02
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	-8.160E+00	5.000E-01	5.400E+00	6.000E+01	1.200E+02
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	-1.191E+01	5.000E-01	4.200E+00	6.000E+01	1.200E+02
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	-8.090E+00	5.000E-01	1.430E+00	6.000E+01	1.200E+02
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	-8.030E+00	5.000E-01	3.380E+00	6.000E+01	1.200E+02

7.2.1.2. Degradation

Nicotine lacks hydrolyzable groups and, therefore, will not undergo abiotic hydrolysis. However, nicotine has the potential to undergo direct photolysis. Nicotine's electronic absorption spectrum shows an intense absorption band at 260-262 nanometers (nm) with some absorption above 290 nm (within the spectrum of energies provided by sunlight) (Sangster & Stuart, 1965). The predicted photochemical half-life for nicotine in air is 1.4 hours. Nicotine can also degrade in surface waters via indirect photolysis by naturally occurring photosensitizers such as dissolved organic matter and hydroxyl radicals. Thus, indirect photolysis can play an important role in the degradation of nicotine.

Biotransformation of nicotine in soils and water-sediment systems has been documented. In soils, nicotine is oxidized by the bacteria *Arthrobacter oxydans* (now known as *Arthrobacter nicotinovarans*). The relative amounts and conditions of biotransformation will vary with soil and bacterial populations. The nature of the transformations in soil is not as well defined as those in animals. It has been demonstrated *in vitro* that the first metabolite of nicotine is 6-hydroxynicotine, which further breaks down to 6-hydroxypseudonicotine

(oxynicotine) and other compounds. Cotinine, which is a major oxidation product of nicotine in the liver, has not been reported to form in soils; however, microorganisms isolated from soils in tobacco fields are capable of degrading nicotine to cotinine in solution (Wang et al., 2012).

Nicotine and its metabolite, cotinine, have been reported to biotransform in sediments (Bradley, Barber, Kolpin, McMahon, & Chapelle, 2007). Under oxidizing conditions nicotine and cotinine degrade completely to CO_2 within 72 days. Under anoxic conditions the biotransformation of nicotine and cotinine is slower. EpiWeb 4.1 predicts half-lives of 37.5 days for nicotine and cotinine in water and 75 days in soil under aerobic conditions.

Data on the transformation products or metabolites of nicotine are very limited. In order to have a common frame of reference, we compared the predicted values for nicotine to the predicted values for the metabolites. Predicted physical-chemical properties of nicotine metabolites and transformation products compare to those of nicotine as follows. Predicted log K_{ow} values range from -1.200 to 0.998. Predicted log K_{oc} ranges from 1.010 to 3.470. Predicted water solubilities range from 5.040×10^3 mg/L to 1.000×10^6 mg/L with nicotine being among the more soluble substances. Predicted Henry's Law Constants range from 3.000×10^{-14} atm-m^3/mole to 3.000×10^{-9} atm-m^3/mole for nicotine and related compounds. Predicted photochemical half-lives range from 1.410 to 7.990 days for nicotine and related compounds. Predicted half-lives in water are all less than 60 days and half-lives in soil are predicted to be less than 120 days. Relative to its metabolites, nicotine is more water soluble and more volatile, and degrades somewhat more quickly. Its behavior was deemed similar enough to that of its metabolites to serve as an appropriate surrogate in the environmental assessment.

7.3. Environmental Effects of Product Released into the Environment

Due to its ecotoxicological relevance, we discuss the effects of nicotine released into the environment in this Section even though nicotine is below concentrations of concern based on the exposure assessments within this environmental assessment.

7.3.1. Nicotine

QSAR predictions in Table 7 were used here as a basis of comparison among nicotine and related compounds and should be taken as qualitative rather than quantitatively definitive. Equations for different classes of compounds used to develop the ECOSAR model within OECD Toolbox V2.38 (OECD, 2012) are of differing reliabilities depending on the dataset used to develop the equation.

Table 7 - Acute Aquatic Toxicity of Nicotine and Related Compounds

CAS	IUPAC Name	Algal 96-EC_{50}	Daphnia 48-hr - EC_{50}	Fish 96-hr LC_{50}
		mg/L	mg/L	mg/L
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	44.70	0.20	4.86
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	17.80	1.92E+03	8.11E+02
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	176.00	5.35E+04	1.11E+04
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	22.20	2.75E+03	1.06E+03
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	131.00	0.22	8.66
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	42.50	38.00	372.00
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	93.30	0.23	7.57
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	69.00	0.24	6.55

Predicted algal 96-hr EC_{50} values range from 17.8 mg/L to 176 mg/L. The predicted EC_{50} for nicotine (CAS 54-11-5) is 44.7 mg/L. While not predicted to be the most toxic compound, nicotine toxicity is within a factor of 2 of the most toxic compounds and likely not significantly different (i.e., within the confidence limits of the prediction). Measured 96-hr EC_{50} values for the toxicity of nicotine to the alga *Selenastrum capricornutum* were 72.9 mg/L for growth and 115 mg/L for biomass (Seckar, et al., 2008). The predicted EC_{50} values for nicotine were lower than the measured values but within a factor of 2.

The predicted 48-hr EC_{50} of nicotine to *Daphnia* is 0.2 mg/L. Predicted toxicity values for the nicotine metabolites range from 0.22 mg/L to 5,350 mg/L. The measured EC_{50} value for *Daphnia pulex* is 0.24 mg/L (Savino & Tanabe, 1989).

The predicted fish 96-hr LC_{50} for nicotine is 4.86 mg/L. The predicted LC_{50} values for metabolites of nicotine range from 6.55 to 11,000 mg/L. Measured LC_{50} values for nicotine toxicity to *Oncorhynchus mykiss* larvae are 4 mg/L (96 hrs), 5 mg/L for fry (60 days), and 6 mg/L for fry (21-31 days).

Terrestrial toxicity data for invertebrates were of limited availability. Because nicotine has a history of use as a pesticide, it is expected that terrestrial invertebrates will be very sensitive to nicotine. Rizvi et al. reported that the 24-hr LD_{50} of nicotine dust was 7.2 micrograms (µg)/nymph for *Dysdercus koenigii (Fabr.)* (Rizvi, Ahmed, & Naqvi, 2012). Additional toxicity data are included on dermal toxicity to the brown tree snake, oral toxicity to rats, and dermal toxicity to rabbits. Terrestrial toxicity to the brown tree snake (*Boiga irregularis*) is reported as 40 milligrams per kilogram (mg/kg) dermally, a dose that killed 100% of snakes (Brooks, Savarie, & Johnston, 1998). The oral LD_{50} dose for nicotine in rats is 50 mg/kg to 60 mg/kg (Klaasen, Amdur, & Doull, 1995). The dermal LD_{50} in rabbits is reported as 140 mg/kg (Lewis, 1996).

7.4. Use of Resources and Energy

Based on the estimated maximum annual market volume of the New Product (from the five-year projected market volume), the use of resources and energy due to the proposed action is expected to be negligible.

7.4.1. Energy Consumption / Greenhouse Gas Emissions

The New Product manufacturing process is (b) (4) The process does not emit greenhouse gas (GHG) pollutants. Energy consumption due to warehousing and distribution is expected to be similar to other consumer products of similar size.

Additional information on energy and resource sustainability efforts are described in Section 7.4.4.

7.4.2. Compliance with ESA and CITES

No critical habitat is affected from materials or ingredients used to manufacture the New Product.

No adverse effects are expected on a species or the critical habitat of a species identified under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) due to the manufacture or marketing of the New Product.

USSTC does not anticipate that any critical habitat or endangered or threatened species will be affected from production of the New Product, or from materials or ingredients used to manufacture the New Product. Altria and USSTC's supply contracts and supplier code of conduct standards support compliance with applicable laws (refer to Section 7.4.4). For more information on supply chain management and responsibility, refer to the Altria website and the Corporate Responsibility Progress Report available at http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html.

The manufacturing facilities are not within or in close proximity to a critical habitat of a threatened or endangered species. USSTC does not expect the manufacture and commercial introduction of the New Product to affect a critical habitat or threaten the existence of listed species or destroy or adversely modify any designated critical habitat for that species. This

is based on a review of critical habitat maps (https://databasin.org/datasets/d579d87eb54f4374a77ea53e7ef66449) created by the U.S. Fish and Wildlife Service (US FWS), which show no critical habitat within close proximity to the manufacturing facilities.

The US FWS's list of species by county (https://www.fws.gov/endangered/) shows that Chesterfield County and Henrico County, Virginia may have one endangered species (Clams – James spinymussel (*Pleurobema collina*)) and three threatened species (Mammals – Northern Long-Eared Bat (*Myotis septentrionalis*; Flowering Plants – Sensitive joint-vetch (*Aeschynomene virginica*), Swamp pink (*Helonias bullata*)). However, these threatened or endangered species are not known to be in the vicinity of the manufacturing facility.

(b) (4)

As described in Section 7.1.1, waste generated as a result of manufacturing the New Product will be considered a hazardous waste (nicotine-containing material) and will be disposed of at waste incineration facilities or will be recycled via a nicotine reclamation facility. As described in Section 7.1.3, the used New Product will be disposed of in the same way as other commercially marketed chewable products. The distribution of waste generated due to disposal of the New Product and packaging is expected to correspond to the pattern of product use in the United States.

(b) (4)

7.4.3. Compliance with Federal, State and Local Environmental Regulations

The (b) (4), where the New Product will be manufactured, comply with the Clean Air Act (CAA), Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). Manufacture of the New Product will not result in changes in compliance with relevant federal, state and local environmental regulations. The facilities' compliance with the CAA, CWA, the RCRA, and other environmental regulations can be assessed on the USEPA's Enforcement and Compliance History Online (ECHO) website.

USSTC maintains an effective Environmental Management System (EMS) which is designed and implemented to integrate environmental programs (including compliance and sustainability) into business operations. Key components of the EMS include: personnel, policy, directives, guidance and training, data management and assessments.

(b) (4)

Regarding waste management, USSTC seeks to (b) (4)

The (b) (4) Regarding hazardous waste management, (b) (4)

(b) (4)

USSTC's long-term contracts with material suppliers, and the purchase order terms and conditions applicable to suppliers without long-term contracts, contain provisions that require compliance with all applicable laws and regulations. Altria's Supplier Code of Conduct also addresses compliance with applicable laws, regulations, and standards, which includes environmental compliance. (b) (4) For more information on supply chain management and responsibility, refer to the Altria website and the Corporate Responsibility Progress Report (http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html).

7.4.4. Environmental Sustainability

Manufacture of the New Product will not affect environmental sustainability at the manufacturing facilities. USSTC has an ongoing initiative to improve environmental sustainability across all facilities. One piece of infrastructure that supports this initiative is the EMS. (b) (4) As a result of these efforts, USSTC expects its overall energy use to decrease over time.

(b) (4) For more information on USSTC's environmental sustainability initiatives, refer to the Altria website and the Corporate Responsibility Progress Report (http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html).

(b) (4)

(b) (4)

(b) (4)

However, the power supplier to these manufacturing facilities is Dominion Energy which has committed to meeting the renewable portfolio goals and standards set by policymakers in Virginia.[16] Dominion Energy has set a renewable energy goal in Virginia to achieve 15% renewable power by 2025.

8. MITIGATION MEASURES

(b) (4) herewith provides the basis for a Finding of No Significant Impact for this environmental assessment of the New Product due to *de minimis* exposure. As such, no additional environmental protection measures, mitigation measures or alternative actions are necessary to address environmental impacts of the New Product.

9. ALTERNATIVES TO THE PROPOSED ACTION

Alternative A (No-action alternative): The no-action alternative is to not allow the marketing of the New Product in the United States.

Alternative B (Proposed action): Issuing a Finding of No Significant Impact due to the proposed action of granting an order finding that the New Product may be introduced or delivered for introduction into interstate commerce under Section 910(c)(1)(A)(i) of the FD&C Act.

The no-action alternative is not expected to significantly change the existing condition. Therefore, the difference between the environmental impacts of these two alternatives is negligible.

[16] Refer to https://www.dominionenergy.com/renewables

10. LIST OF PREPARERS

In accordance with 40 CFR 1502.17, this section includes a list of names and qualifications (including position/title, education, experience, and expertise) of individuals who were primarily responsible for preparing and reviewing this environmental assessment. No Agencies or persons besides subject matter experts within (b) (4) and ALCS were consulted. However, feedback from FDA on prior submissions and examples of Environmental Assessments posted by FDA were considered in developing this assessment.

(b) (4)

Education: M.S. in Chemical Engineering; MBA

Years of Experience: > 25 years in environmental consulting

Qualifications: Environmental assessments and audits, environmental risk assessment, environmental compliance & assurance activities, air quality, and product stewardship and sustainability.

(b) (4)

Education: B.S. in Chemistry; M.S. in Environmental Engineering

Years of Experience: > 25 years in environmental management and regulatory activities

Qualifications: Environmental assessments, environmental risk assessment, environmental compliance & assurance activities, life cycle assessment, engineering design of pollution control measures, and product stewardship and sustainability.

(b) (4)

Education: B.S. in Mechanical Engineering

Years of Experience: 25 years in environmental management and regulatory activities

Qualifications: Environmental assessments and audits, environmental risk assessment, environmental compliance & assurance activities, air quality, Toxic Substances Control Act (TSCA) compliance, and product stewardship and sustainability.

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12. APPENDICES

As a final measure of substantiation for the minimal environmental risk associated with the use of the New Product, (b) (4) has included the following Appendices.

Data summaries provide a brief summation of the available physico-chemical properties, toxicology and ecotoxicology data for the product ingredients and are included in Confidential Appendix 5-1-2. Data contained in the attached summaries are from publicly available compilations from sources including the USEPA and the European Chemicals Agency (ECHA). Specific references are noted as appropriate.

Additional information regarding the regulatory status of product ingredients are provided in Confidential Appendix 5-1-3 to further substantiate FDA's acceptance of these substances from an environmental perspective.

13. CERTIFICATION

(b) (4)

APPENDIX 5-1-2 – ENVIRONMENTAL ASSESSMENT
TRADE SECRET/CONFIDENTIAL COMMERCIAL INFORMATION RESPONSE
TO ADVICE/INFORMATION REQUEST FOR VERVE® CHEWS BLUE MINT

Data Summaries

Empty boxes in Data Summaries are intentionally left blank

Data contained in the attached summaries are from readily available compilations from sources including the US Environmental Protection Agency (EPA) and the European Chemicals Agency (ECHA). Specific references are noted as appropriate.

Ingredient ID#	Ingredient Name	Link
1	(b) (4)	Ingredient 1.pdf
2		Ingredient 2.pdf
3		Ingredient 3.pdf
4		Ingredient 4.pdf
5		Ingredient 5.pdf
7		Ingredient 7.pdf
8		Ingredient 8.pdf
9		Ingredient 9.pdf
11		Ingredient 11.pdf
12		Ingredient 12.pdf
13		Ingredient 13.pdf
14		Ingredient 14.pdf
16		Ingredient 16.pdf
17		Ingredient 17.pdf
18		Ingredient 18.pdf
19		Ingredient 19.pdf
20		Ingredient 20.pdf
21		Ingredient 21.pdf

(b) (4)

Ingredient ID#	Ingredient Name	Link
24	(b) (4)	Ingredient 24.pdf
25		Ingredient 25.pdf
26		Ingredient 26.pdf
27		Ingredient 27.pdf
28		Ingredient 28.pdf
29		Ingredient 29.pdf
30		Ingredient 30.pdf
32		Ingredient 32.pdf
33		Ingredient 33.pdf
34		Ingredient 34.pdf
35		Ingredient 35.pdf
36		Ingredient 36.pdf
37		Ingredient 37.pdf
38		Ingredient 38.pdf
39		Ingredient 39.pdf
40		Ingredient 40.pdf
41		Ingredient 41.pdf
42		Ingredient 42.pdf
43		Ingredient 43.pdf
44		Ingredient 44.pdf
46		Ingredient 46.pdf

Ingredient ID#	Ingredient Name	Link
47	(b)(4)	Ingredient 47.pdf
49		Ingredient 49.pdf
50		Ingredient 50.pdf
54		Ingredient 54.pdf
55		Ingredient 55.pdf
56		Ingredient 56.pdf
57		Ingredient 57.pdf
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64		Ingredient 64.pdf
65		Ingredient 65.pdf
67		Ingredient 67.pdf
69		Ingredient 69.pdf
71		Ingredient 71.pdf
72		Ingredient 72.pdf
73		Ingredient 73.pdf
74		Ingredient 74.pdf
75		Ingredient 75.pdf

Ingredient ID#	Ingredient Name	Link
76	(b) (4)	Ingredient 76.pdf
78		Ingredient 78.pdf

(b) (4)

ENVIRONMENTAL ASSESSMENT
TRADE SECRET/CONFIDENTIAL COMMERCIAL INFORMATION
FOR THE PRODUCT IDENTIFIED AS VERVE® CHEWS GREEN MINT

Memorandum

To:	Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC
From:	(b) (4)
Date:	May 24, 2018
Subject:	Environmental Assessment for the Premarket Tobacco Product Application for the Product Identified as VERVE® Chews Green Mint

This environmental assessment was prepared in accordance with 21 CFR 25.40, the Food and Drug Administration's (FDA's or Agency's) regulation implementing the National Environmental Policy Act of 1969. Under NEPA, "all applications or petitions requesting Agency action require the submission of an environmental assessment or a claim of categorical exclusion."[1]

(b) (4) respectfully submits the following environmental assessment in support of the *Premarket Tobacco Product Application (PMTA)* for the product identified as *VERVE® Chews Green Mint* (referred to throughout this assessment as the "New Product") pursuant to 21 CFR 25.20 because there is no applicable categorical exclusion for this type of application.

This environmental assessment was conducted in accordance with 21 CFR 25.40 and relevant aspects of FDA technical guidance documents including:

- *Environmental Considerations for Tobacco Product Applications Submitted to CTP, presented by Cristi Stark, M.S., Associate Director for Science Policy, Office of Science, CTP, FDA (August 2016);*
- *Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I (March 2001); and*
- *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).*

[1] 21 CFR 25.15(a)

This environmental assessment was prepared at the direction of Altria Client Services LLC (ALCS) on behalf of U.S. Smokeless Tobacco Company LLC (USSTC), a wholly owned subsidiary of Altria Group Inc. The potential aquatic, atmospheric, and terrestrial environmental impacts of FDA's approval of the PMTA and subsequent marketing of the New Product were considered using a conservative set of assumptions. The assessment identified no significant environmental risks, and a Finding of No Significant Impact by FDA is warranted for the environmental assessment of the New Product.

This memorandum contains trade secret and confidential commercial information that USSTC considers to be proprietary and highly sensitive, and which is protected from disclosure under the Food, Drug and Cosmetic Act §§ 301(j) and 906(c) (21 U.S.C. §§ 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. § 1905), the Freedom of Information Act (5 U.S.C. § 552), and FDA's implementing regulations, 21 CFR Part 20. If FDA receives a request for these records and tentatively determines that any portion of this submission is disclosable, USSTC requests that FDA provide notice and opportunity for USSTC to object to any disclosure in accordance with 21 CFR § 20.47 and 21 CFR § 20.61. USSTC reserves all of its legal rights to protect against public disclosure of its trade secret and confidential commercial information and to seek legal recourse against anyone who discloses such information without legal authorization.

1. DATE

May 24, 2018

2. NAME OF APPLICANT/SUBMITTER

Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC

3. ADDRESS

2325 Bells Road, Richmond, Virginia 23234

4. MANUFACTURER

U. S. Smokeless Tobacco Company LLC

5. DESCRIPTION OF PROPOSED ACTION

The proposed action is for FDA to issue a market authorization order under Section 910(c)(1)(A)(i) of the Food, Drug and Cosmetic Act (FD&C Act)[2] to introduce the New Product into interstate commerce. Through a PMTA for the New Product, USSTC is requesting approval from FDA to introduce the New Product into interstate commerce for commercial distribution in the United States. USSTC is including this environmental assessment with its submittal of the PMTA to FDA for the New Product.

6. IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

6.1. Type of Tobacco Product

Verve® chews are a chewable, non-dissolvable, tobacco-derived nicotine product (known as an oral nicotine-delivery product). The chewable form of the New Product has a soft, flexible texture.

6.2. Estimated Market Volumes

The following table presents the estimated first-year and fifth-year market volumes for the New Product. These estimated market volumes form the basis for the environmental exposure estimates provided in this assessment.

Table 1 – Estimated First-Year and Fifth-Year Market Volumes for the New Product

Name	Unit	New Product	
		First-Year Projected Market Volume	Fifth-Year Projected Market Volume
VERVE® Chews Green Mint	Tubes[3]		(b) (4)
	Metric Tons		

6.3. Product Composition

The New Product contains tobacco-derived nicotine, (b)(4), non-tobacco cellulose fiber, flavorings, texture modifiers, binders and colorants.

[2] 21 U.S.C. 387j
[3] There are 12 chews in one tube.

6.3.1. *Product*

The formulation of the New Product is given in the following table. All values are reported in milligrams (mg).

Table 2 – Product Formulation

ID #[4]	CAS Number	Substance	Amount per Piece (mg)
1			(b) (4)
2			
3			
4			
5			
7			
8			
9			
11			
12			
14			
16			
17			
18			
19			
20			

[4] The ID# is a unique number for each ingredient; it corresponds to the list of ingredients in Confidential Appendix 5-2-2.

Table 2 – Product Formulation

ID #[1]	CAS Number	Substance	Amount per Piece (mg)
21			(b) (4)
24			
25			
26			
28			
29			
30			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			

Table 2 – Product Formulation

ID #[1]	CAS Number	Substance	Amount per Piece (mg)
46			(b) (4)
47			
48			
49			
50			
52			
53			
55			
56			
57			
60			
61			
62			
63			
64			
65			
67			
68			
69			
71			

Table 2 – Product Formulation

ID #[4]	CAS Number	Substance	Amount per Piece (mg)
72			(b) (4)
73			
74			
75			
76			
78			

6.3.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

6.3.2. Packaging

Packaging material for the New Product comprises the following components, with weight represented on a per product basis. The individual chews (12) are packaged in a Tube which contains a tube, button (lid), label and a shrink band. USSTC has designed all packaging materials to meet FDA's standard for direct and indirect food additives set forth in Title 21 of the Code of Federal Regulations (CFR).

Table 3 – Characterization and Weight of Packaging Materials[5]

Packaging Component	Package Composition	Weight (grams)
Tube		(b) (4)
Button		
Label		

[5] There are 12 chews per tube, 5 tubes per carton and 5 cartons per case.

Table 3 – Characterization and Weight of Packaging Materials[5]

Packaging Component	Package Composition	Weight (grams)
(b)(4)		

6.4. Location of Manufacture

The New Product will be manufactured at U.S. Smokeless Tobacco Products LLC, located at (b) (4) U.S. Smokeless Tobacco Products LLC is a business entity of United States Smokeless Tobacco Company (USSTC). The (b)(4) for the New Product.

6.5. Location of Use

USSTC intends to market the New Product to adult consumers throughout the United States.

6.6. Disposal Sites

The distribution of waste generated due to disposal of the New Product and/or packaging is expected to correspond to the pattern of product use. Disposed materials will either enter the recycling stream or be disposed of in municipal solid waste (MSW) landfills or as litter. Additional information is provided in Section 7.1.3 below.

7. ENVIRONMENTAL ISSUES

7.1. Introduction of the Product into the Environment

7.1.1. As a Result of Manufacture

No significant environmental impacts are anticipated as a result of manufacturing the New Product. (b) (4)

(b) (4)

According to the U.S. Environmental Protection Agency (USEPA)'s most recent National Biennial Report data (https://rcrainfo.epa.gov/rcrainfoweb/action/modules/br/summary/view), 33,646,921 tons of hazardous wastes were generated across the United States in 2015. Of this amount, over 2,688,613 tons were incinerated or used (combusted) for energy recovery. Assuming the entire production volume is disposed of by the manufacturing facility, the New Product

is expected to generate up to (b) (4) of hazardous waste per year.[6] This represents up to (b) (4) of the total hazardous waste in the country and up to (b) (4) of the total hazardous waste treated by incineration or used (combusted) for energy recovery in the country. Thus, the contribution of the New Product to total hazardous waste generated and treated by incineration (or energy recovery) annually in the United States is miniscule. Therefore, additional resources (e.g., new incineration or similar treatment facilities, etc.) will not be required for disposal of the New Product.

Section 7.1.3 addresses the solid waste generation expected to result from use of the New Product. The New Product following use by consumers is an exempt household hazardous waste and is not subject to regulation as hazardous waste.

No significant environmental impacts are anticipated as a result of manufacturing the New Product.

7.1.2. As a Result of Use

The aquatic environment is the primary compartment of concern for environmental releases resulting from use of the New Product. The New Product is used orally. Therefore, exposure to the terrestrial and atmospheric environments is not anticipated.

7.1.2.1. Aquatic

7.1.2.1.1. Product

The New Product ingredients are expected to be released primarily to the aquatic environment via excretion as a result of product use. To quantify the anticipated amount of each chemical substance contained in the New Product to the aquatic environment, (b) (4) calculated the annual load (kilograms per year, or kg/yr) and the aquatic expected introduction concentration (EIC) (micrograms per liter, or µg/L). (b) (4) applied the approach FDA established for human drugs and biologics to calculate the aquatic EIC as follows:

[6] Maximum US tons of MSW per year = A*B*C; where A = Maximum Annual Shipping Quantity between 1st Year and 5th Year (g), B = Weight of product (g), C = 1 / 907,185 g/US Ton (Conversion from g to US Tons)

EIC-aquatic (ppb or µg/L) =A * B * C * D, where

A=kg/yr produced,

B=1/1.071x10^{11} L/day entering POTW (Publicly Owned Treatment Works facility)

(Source: Clean Watersheds Needs Survey (NWNS) 2012 Data and Reports, Detailed Listing of Waste Water Treatment Plant Flows for the Nation accessible at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:4:::::RP::),

C=year/365,

D=10^{9} µg/kg

In calculating the aquatic EIC values, (b) (4) maintained the following conservative assumptions that were established in FDA guidance:[7]

- The kg/year produced is based on the highest quantity expected to be produced for direct use in any of the next five years;
- All product produced in a year is used and enters the POTW system [The ingredients are absorbed by the human body during use and 100% of the ingredients are then excreted to sanitary sewer and to treatment within the POTW];[8]
- New Product usage occurs throughout the United States in proportion to the population and amount of wastewater generated;
- No dilution occurs in receiving waters; and
- There is no metabolism.

The results of these calculations were compared to FDA's established concentration of concern (1 µg/L or ppb). As described in its 2001 technical guidance document, *Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I*, FDA considers this value to be below the level shown to have adverse effects in aquatic ecotoxicity studies with human drugs. This was deemed appropriate for the current assessment as No Observed Effect Concentration (NOEC) values for each substance, where available, are greater than 1 µg/L or ppb.

A brief summary of publicly available fate and effects data for each ingredient of the New Product is provided in Confidential Appendix 5-2-2 for reference.

[7] Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)

[8] (b) (4)

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
		(b) (4)

[9] (annual production forecast) x (relative amount in formulation)

[10] EI Caquatic (ppb or µg/L)=A*B*C*D; where A=kg/yr produced, B=1/1.071x10^{11} L/day entering POTW (Source: Clean Watersheds Needs Survey (NWNS) 2012 Data and Reports, Detailed Listing of Waste Water Treatment Plant Flows for the Nation accessible at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:4:::RP::), C=year/365, D=10^{9} µg/kg

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
		(b) (4)

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EiC (µg/L)[10]
		(b) (4)

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
(b) (4)		

(b) (4) noted that in every case, the aquatic EIC is (b) (4) at the point of entry into the aquatic environment, which is below the relevant concentration of concern identified in FDA guidance.

7.1.2.1.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

In Table 4, (b) (4) noted that the EIC calculated for nicotine is (b)(4) at the point of entry into the aquatic environment and therefore below FDA's established concentration of concern. Nonetheless, fate and effects data for nicotine are discussed in detail in Sections 7.2 and 7.3 of this assessment.

7.1.2.1.2. Packaging

Packaging is not intended or expected to release chemical substances during use. Releases as a result of disposal are discussed in Section 7.1.3 of this assessment.

7.1.3. As a Result of Disposal

Following use by consumers, the New Product is an exempt household waste and is not subject to regulation as hazardous waste. The New Product will be disposed of in MSW landfills or as litter. The associated packaging materials will either be recycled or be disposed of in MSW landfills or as litter. The New Product will be disposed of in the same way as other commercially marketed consumer chewable products (e.g., chewing gums or chewable tablets). The distribution of waste generated due to disposal of the New Product and packaging is expected to correspond to the pattern of product use throughout the United States.

Disposal following use of the New Product is not expected to require additional resources for waste disposal. The terrestrial environment is the primary compartment of concern for environmental releases of the New Product as a result of disposal. Any release to the aquatic environment as a result of disposal is addressed by the calculations conducted in Section 7.1.2.

7.1.3.1. Disposal of the Product Following Use

According to the U.S. Environmental Protection Agency (USEPA) document, *Advancing Sustainable Materials Management: 2014 Fact Sheet Assessing Trends in Material Generation, Recycling, Composting, Combustion with Energy Recovery and Landfilling in the United States*, 258 million tons of MSW were generated across the United States in 2014. Of this, over 89 million tons (34.6%) were recycled and composted, more than 136 million tons (52.6%) were discarded in a landfill, and more than 33 million tons (12.8%) were combusted with energy recovery (USEPA, 2016a). Chewable nicotine products (oral nicotine-delivery products) are not expected to be recycled.

Assuming the entire production volume is disposed of in a landfill, the New Product is expected to generate up to (b) (4) of MSW per year.[11] This represents up to (b) (4) of the total MSW in the country and up to (b) (4) of MSW that is disposed of in landfills in the country. Thus, the contribution of the New Product to total MSW disposed annually in

[11] Maximum US tons of MSW per year = A*B*C; where A = Maximum Annual Shipping Quantity between 1st Year and 5th Year (g), B = Weight of product (g), C = 1 / 907,185 g/US Ton (Conversion from g to US Tons)

the United States is miniscule. Therefore, additional resources (e.g., new landfills, recycling centers, etc.) will not be required for disposal following use of the New Product.

Proper disposal will be to landfill and not directly to the terrestrial environment. Disposal to MSW landfills will not result in adverse effects to the environment based on landfill design and regulatory requirements. Disposed waste streams within a landfill are prevented from entering the environment and ultimately landfill leachate is treated and/or sent to POTWs for effective treatment.

Disposal following use of the New Product is not expected to result in new or additional compounds emitted to the environment. USSTC anticipates the New Product will be disposed of following use in the same way as other commercially marketed consumer chewable products (e.g., chewing gums or chewable tablets). The distribution of waste generated due to disposal of the New Product is expected to correspond to the same pattern of product use. No new or additional environmental effects, as defined within 40 CFR 1508.8, are anticipated. However, improper disposal may occur. The calculations provided in Section 7.1.3.2 conservatively address product that is inappropriately disposed of directly to the environment.

7.1.3.2. Terrestrial

7.1.3.2.1. Product

Introduction of the New Product to the terrestrial environment was calculated as surface density. Absent guidance from FDA on the appropriate duration to be used for this calculation and because it is conservatively assumed there is no metabolism or depletion in the environment, a timeframe had to be selected. Therefore, the terrestrial surface density of each ingredient was calculated on a per day basis.

The daily terrestrial surface density values are presented in following table as the production tonnage distributed across the surface area of the United States per day (nanograms per square meter per day, or ng/m^2 per day). These values were based on the very conservative assumptions that the entire production volume was introduced to commerce and that the New Product is released to the terrestrial environment in its complete and unused state. The calculation is shown in the footnote for the table.

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m² per day)[12]
	(b) (4)

[12] Daily Surface Density (ng/m² per day) = A*B*C*D*E; where A = mg/yr produced, B = 1/9.158x10⁶ km² surface area of the United States, C = year/365 days, D = 10⁶ km²/m², E = 10⁶ ng/mg

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)
[redacted]	(b) (4)

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m² per day)
[redacted]	(b) (4)

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m² per day)[14]
[redacted]	(b) (4)

The daily terrestrial surface density values presented as a production tonnage distributed across the surface area of the United States are (b) (4) ng/m² per day as determined using the calculations shown in the footnote in the table above. The values are so small that exposure to the New Product in the terrestrial environment as described here would not have a significant effect.

Based on the mass of non-nicotine ingredients shown in Table 2 and publicly available environmental fate and effects data, a single used or unused chew that is improperly disposed is not expected to cause localized effects to the terrestrial environment. Adverse effects are highly unlikely because improper disposal of chews should occur only on rare occasions and the non-nicotine ingredients are expected to exhibit a low order of environmental toxicity.

7.1.3.2.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

The daily terrestrial surface density value for nicotine as the production tonnage distributed across the surface area of the United States per day (ng/m² per day)[15] is (b) (4) ng/m² per

[15] Daily Surface Density (ng/m² per day) = A*B*C*D*E; where A = mg/yr produced, B = 1/9.158x10⁶ km² surface area of the United States, C = year/365, D = 10⁻⁶ km²/m², E = 10⁶ ng/mg

day. This was based on the very conservative assumptions that the entire production volume was introduced to commerce and that the New Product is released to the terrestrial environment in its complete and unused state.

(b) (4)

7.1.3.3. Disposal of Packaging Following Use

The New Product's packaging is expected to be disposed of following use in the same way as packaging from other commercially marketed consumer chewable products. The distribution of waste generated due to disposal of packaging is expected to correspond to the same pattern of product use.

According to the USEPA document, *Advancing Sustainable Materials Management: 2014 Fact Sheet Assessing Trends in Material Generation, Recycling, Composting, Combustion with Energy Recovery and Landfilling in the United States*, 258 million tons of MSW were generated across the United States in 2014. Of this, over 89 million tons (34.6%) were recycled and composted, more than 136 million tons (52.6%) were discarded in a landfill, and more than 33 million tons (12.8%) were combusted with energy recovery (USEPA, 2016a). Assuming all of the New Product packaging is disposed of to landfill, packaging from the New Product is expected to generate up to (b) tons of MSW per year[14]. This represents up to (b) (4) of the total MSW in the country and up to (b) (4) of MSW that is disposed of in landfills in the country. Thus, the contribution of the New Product's packaging to total MSW disposed annually in the United States is miniscule. Therefore, disposal of the New Product's

[14] (b) (4)

packaging following use of the New Product is not expected to require additional resources (e.g., new landfills, recycling centers, etc.) for waste disposal.

Disposal of packaging following use of the New Product is not expected to result in new or additional compounds emitted to the environment. The materials used in the packaging of the New Product (b) (4) (b) (4) are common packaging materials used for consumer products in general. Proper disposal will be to landfill and not directly to the terrestrial environment. Disposal to MSW landfills will not result in adverse effects to the environment based on landfill design and regulatory requirements. The same or similar compounds and types of emissions are anticipated from disposal of the packaging of the New Product as those associated with disposal of the packaging of other consumer chewable products or consumer products in general. Thus, no new or additional environmental effects, as defined within 40 CFR 1508.8, are anticipated.

7.2. Fate of Product Released into the Environment

Due to its ecotoxicological relevance, we discuss the fate of nicotine released into the environment in this Section even though nicotine is below concentrations of concern based on the exposure assessments within this environmental assessment.

7.2.1. Nicotine

Quantitative Structure Activity Relationships (QSARs) have been used to describe the physical-chemical properties of nicotine and to provide predicted aquatic toxicity values to support the use of nicotine as a marker compound. Acceptable QSARs are not available to predict toxicity to terrestrial organisms. All QSAR predictions were determined using the USEPA's EpiWeb 4.1.[15]

7.2.1.1. Physical Chemical Properties

The physical-chemical properties of pure nicotine (CAS 54-11-5) and its metabolites are presented in the following table. Nicotine's physical-chemical properties can be used to assess the fate of nicotine introduced into the environment.

[15] The EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical/chemical property and environmental fate estimation programs developed by the USEPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). EPI Suite™ uses a single input to run the following estimation programs: KOWWIN™, AOPWIN™, HENRYWIN™, MPBPWIN™, BIOWIN™, BioHCwin, KOCWIN™, WSKOWWIN™, WATERNT™, BCFBAF™, HYDROWIN™, KOAWIN and AEROWIN™, and the fate models WVOLWIN™, STPWIN™ and LEV3EPI™. ECOSAR™, which estimates ecotoxicity, is also included in EPI Suite™ (USEPA, 2016b).

Nicotine introduced into water will stay mainly in water and will not readily partition to air based on its low Henry's Law Constant ($3x10^{-9}$ atmospheres – cubic meters per mole or atm-m^3/mole) and negative air/water partitioning coefficient (K_{aw} = -6.910) (USEPA, 2016b). Nicotine in water should not bioaccumulate or bioconcentrate in aquatic organisms (measured log K_{ow} = 1.17) (Hansch, Hoekman, Leo, Zhang, & Li, 1995). The predicted bioconcentration factor (log BCF) for nicotine of 0.440 supports this conclusion.

Nicotine introduced into the soil can volatilize to air based on the vapor pressure of 0.032 mm Hg (Boublik, 1984). However, the extent to which it actually volatilizes will depend on its sorption. The log K_{oc} predicted at neutral pH is 2.720 and indicates that nicotine in soil has moderate mobility. The mobility of nicotine, a weak acid (pK_a 8.5), is pH dependent and will increase at alkaline pH. Because nicotine is highly soluble (predicted solubility $1.000x10^6$ milligrams per liter, or mg/L) and has a negative K_{aw}, it will most likely partition to soil pore-water rather than air.

Table 6a – Predicted Physical-Chemical Properties of Nicotine and Related Compounds

CAS	IUPAC Name	Water Solubility	Vapour Pressure	Henry's Law Constant	Log K_{ow}	log K_{oc}	Log K_{oa}
		mg/L	mm Hg	atm-m^3/mol			
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	1 000E+06	3 200E-02	3 000E-09	9 980E-01	2 720E+00	8 080E+00
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	9 990E+05	3 810E-04	3 330E-12	3 400E-01	2 110E+00	8 038E+00
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	1 000E+06	2 160E-07	5 200E-13	-1 200E+00	1 010E+00	9 190E+00
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	1 000E+06	1 660E-05	1 520E-12	-3 000E-01	2 100E+00	9 900E+00
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	6 030E+05	5 120E-04	1 970E-10	3 210E-01	3 200E+00	8 480E+00
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	5 040E+03	5 130E-07	3 000E-14	6 860E-01	2 190E+00	1 260E+01
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	3 060E+05	6 040E-05	1 970E-10	5 970E-01	3 470E+00	8 690E+00
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	1 960E+05	6 680E-05	8 580E-11	8 120E-01	3 470E+00	8 850E+00

Table 6b – Predicted Physical-Chemical Properties of Nicotine and Related Compounds

CAS	IUPAC Name	Log K_{aw}	BCF	Photo-chemical half-life	Half-life in water	Half-life in soil
				hrs	days	days
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	-6.910E+00	4.400E-01	1.410E+00	3.750E+01	7.500E+01
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	-8.040E+00	5.000E-01	4.900E+00	3.750E+01	7.500E+01
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	-1.067E+01	5.000E-01	4.300E+00	3.750E+01	7.500E+01
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	-1.027E+01	5.000E-01	7.990E+00	6.000E+01	1.200E+02
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	-8.160E+00	5.000E-01	5.400E+00	6.000E+01	1.200E+02
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	-1.191E+01	5.000E-01	4.200E+00	6.000E+01	1.200E+02
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	-8.090E+00	5.000E-01	1.430E+00	6.000E+01	1.200E+02
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	-8.030E+00	5.000E-01	3.380E+00	6.000E+01	1.200E+02

7.2.1.2. Degradation

Nicotine lacks hydrolyzable groups and, therefore, will not undergo abiotic hydrolysis. However, nicotine has the potential to undergo direct photolysis. Nicotine's electronic absorption spectrum shows an intense absorption band at 260-262 nanometers (nm) with some absorption above 290 nm (within the spectrum of energies provided by sunlight) (Sangster & Stuart, 1965). The predicted photochemical half-life for nicotine in air is 1.4 hours. Nicotine can also degrade in surface waters via indirect photolysis by naturally occurring photosensitizers such as dissolved organic matter and hydroxyl radicals. Thus, indirect photolysis can play an important role in the degradation of nicotine.

Biotransformation of nicotine in soils and water-sediment systems has been documented. In soils, nicotine is oxidized by the bacteria *Arthrobacter oxydans* (now known as *Arthrobacter nicotinovarans*). The relative amounts and conditions of biotransformation will vary with soil and bacterial populations. The nature of the transformations in soil is not as well defined as those in animals. It has been demonstrated *in vitro* that the first metabolite of nicotine is 6-hydroxynicotine, which further breaks down to 6-hydroxypseudonicotine (oxynicotine) and other compounds. Cotinine, which is a major oxidation product of nicotine in the liver, has not been reported to form in soils; however, microorganisms isolated from soils in tobacco fields are capable of degrading nicotine to cotinine in solution (Wang et al., 2012).

Nicotine and its metabolite, cotinine, have been reported to biotransform in sediments (Bradley, Barber, Kolpin, McMahon, & Chapelle, 2007). Under oxidizing conditions nicotine and cotinine degrade completely to CO_2 within 72 days. Under anoxic conditions the biotransformation of nicotine and cotinine is slower. EpiWeb 4.1 predicts half-lives of 37.5 days for nicotine and cotinine in water and 75 days in soil under aerobic conditions.

Data on the transformation products or metabolites of nicotine are very limited. In order to have a common frame of reference, we compared the predicted values for nicotine to the predicted values for the metabolites. Predicted physical-chemical properties of nicotine metabolites and transformation products compare to those of nicotine as follows. Predicted log K_{ow} values range from -1.200 to 0.998. Predicted log K_{oc} ranges from 1.010 to 3.470. Predicted water solubilities range from 5.040×10^3 mg/L to 1.000×10^6 mg/L with nicotine being among the more soluble substances. Predicted Henry's Law Constants range from 3.000×10^{-14} atm-m^3/mole to 3.000×10^{-9} atm-m^3/mole for nicotine and related compounds. Predicted photochemical half-lives range from 1.410 to 7.990 days for nicotine and related compounds. Predicted half-lives in water are all less than 60 days and half-lives in soil are predicted to be less than 120 days. Relative to its metabolites, nicotine is more water soluble and more volatile, and degrades somewhat more quickly. Its behavior was deemed similar

enough to that of its metabolites to serve as an appropriate surrogate in the environmental assessment.

7.3. Environmental Effects of Product Released into the Environment

Due to its ecotoxicological relevance, we discuss the effects of nicotine released into the environment in this Section even though nicotine is below concentrations of concern based on the exposure assessments within this environmental assessment.

7.3.1. Nicotine

QSAR predictions in Table 7 were used here as a basis of comparison among nicotine and related compounds and should be taken as qualitative rather than quantitatively definitive. Equations for different classes of compounds used to develop the ECOSAR model within OECD Toolbox V2.38 (OECD, 2012) are of differing reliabilities depending on the dataset used to develop the equation.

Table 7 - Acute Aquatic Toxicity of Nicotine and Related Compounds

CAS	IUPAC Name	Algal 96-EC_{50}	Daphnia 48-hr - EC_{50}	Fish 96-hr LC_{50}
		mg/L	mg/L	mg/L
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	44.70	0.20	4.86
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	17.80	1.92E+03	8.11E+02
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	176.00	5.35E+04	1.11E+04
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	22.20	2.75E+03	1.06E+03
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	131.00	0.22	8.66
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	42.50	38.00	372.00
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	93.30	0.23	7.57
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	69.00	0.24	6.55

Predicted algal 96-hr EC_{50} values range from 17.8 mg/L to 176 mg/L. The predicted EC_{50} for nicotine (CAS 54-11-5) is 44.7 mg/L. While not predicted to be the most toxic compound, nicotine toxicity is within a factor of 2 of the most toxic compounds and likely not significantly different (i.e., within the confidence limits of the prediction). Measured 96-hr EC_{50} values for the toxicity of nicotine to the alga *Selenastrum capricornutum* were 72.9 mg/L for growth and 115 mg/L for biomass (Seckar, et al., 2008). The predicted EC_{50} values for nicotine were lower than the measured values but within a factor of 2.

The predicted 48-hr EC_{50} of nicotine to *Daphnia* is 0.2 mg/L. Predicted toxicity values for the nicotine metabolites range from 0.22 mg/L to 5,350 mg/L. The measured EC_{50} value for *Daphnia pulex* is 0.24 mg/L (Savino & Tanabe, 1989).

The predicted fish 96-hr LC_{50} for nicotine is 4.86 mg/L. The predicted LC_{50} values for metabolites of nicotine range from 6.55 to 11,000 mg/L. Measured LC_{50} values for nicotine toxicity to *Oncorhynchus mykiss* larvae are 4 mg/L (96 hrs), 5 mg/L for fry (60 days), and 6 mg/L for fry (21-31 days).

Terrestrial toxicity data for invertebrates were of limited availability. Because nicotine has a history of use as a pesticide, it is expected that terrestrial invertebrates will be very sensitive to nicotine. Rizvi et al. reported that the 24-hr LD_{50} of nicotine dust was 7.2 micrograms (µg)/nymph for *Dysdercus koenigii (Fabr.)* (Rizvi, Ahmed, & Naqvi, 2012). Additional toxicity data are included on dermal toxicity to the brown tree snake, oral toxicity to rats, and dermal toxicity to rabbits. Terrestrial toxicity to the brown tree snake (*Boiga irregularis*) is reported as 40 milligrams per kilogram (mg/kg) dermally, a dose that killed 100% of snakes (Brooks, Savarie, & Johnston, 1998). The oral LD_{50} dose for nicotine in rats is 50 mg/kg to 60 mg/kg (Klaasen, Amdur, & Doull, 1995). The dermal LD_{50} in rabbits is reported as 140 mg/kg (Lewis, 1996).

7.4. Use of Resources and Energy

Based on the estimated maximum annual market volume of the New Product (from the five-year projected market volume), the use of resources and energy due to the proposed action is expected to be negligible.

7.4.1. Energy Consumption / Greenhouse Gas Emissions

The New Product manufacturing process is (b) (4) [redacted]. The process does not emit greenhouse gas (GHG) pollutants. Energy consumption due to warehousing and distribution is expected to be similar to other consumer products of similar size.

Additional information on energy and resource sustainability efforts are described in Section 7.4.4.

7.4.2. Compliance with ESA and CITES

No critical habitat is affected from materials or ingredients used to manufacture the New Product.

No adverse effects are expected on a species or the critical habitat of a species identified under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) due to the manufacture or marketing of the New Product.

USSTC does not anticipate that any critical habitat or endangered or threatened species will be affected from production of the New Product, or from materials or ingredients used to manufacture the New Product. Altria and USSTC's supply contracts and supplier code of conduct standards support compliance with applicable laws (refer to Section 7.4.4). For more information on supply chain management and responsibility, refer to the Altria website and the Corporate Responsibility Progress Report available at http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html.

The manufacturing facilities are not within or in close proximity to a critical habitat of a threatened or endangered species. USSTC does not expect the manufacture and commercial introduction of the New Product to affect a critical habitat or threaten the existence of listed species or destroy or adversely modify any designated critical habitat for that species. This is based on a review of critical habitat maps (https://databasin.org/datasets/d579d87eb54f4374a77ea53e7ef66449) created by the U.S. Fish and Wildlife Service (US FWS), which show no critical habitat within close proximity to the manufacturing facilities.

The US FWS's list of species by county (https://www.fws.gov/endangered/) shows that Chesterfield County and Henrico County, Virginia may have one endangered species (Clams – James spinymussel (*Pleurobema collina*)) and three threatened species (Mammals – Northern Long-Eared Bat (*Myotis septentrionalis*; Flowering Plants – Sensitive joint-vetch (*Aeschynomene virginica*), Swamp pink (*Helonias bullata*)). However, these threatened or endangered species are not known to be in the vicinity of the manufacturing facility.

(b) (4)

As described in Section 7.1.1, waste generated as a result of manufacturing the New Product will be considered a hazardous waste (nicotine-containing material) and will be disposed of at waste incineration facilities or will be recycled via a nicotine reclamation facility. As described in Section 7.1.3, the used New Product will be disposed of in the same way as other commercially marketed chewable products. The distribution of waste generated due to disposal of the New Product and packaging is expected to correspond to the pattern of

product use in the United States.

(b) (4)

7.4.3. Compliance with Federal, State and Local Environmental Regulations

The (b) (4), where the New Product will be manufactured, comply with the Clean Air Act (CAA), Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). Manufacture of the New Product will not result in changes in compliance with relevant federal, state and local environmental regulations. The facilities' compliance with the CAA, CWA, the RCRA, and other environmental regulations can be assessed on the USEPA's Enforcement and Compliance History Online (ECHO) website.

USSTC maintains an effective Environmental Management System (EMS) which is designed and implemented to integrate environmental programs including (compliance and sustainability) into business operations. Key components of the EMS include: personnel, policy, directives, guidance and training, data management and assessments.

(b) (4)

Regarding waste management, USSTC seeks to (b) (4)

(b) (4)

The (b) (4) Regarding hazardous waste management, (b) (4)

USSTC's long-term contracts with material suppliers, and the purchase order terms and conditions applicable to suppliers without long-term contracts, contain provisions that require compliance with all applicable laws and regulations. Altria's Supplier Code of Conduct also addresses compliance with applicable laws, regulations, and standards, which includes environmental compliance. (b) (4) For more information on supply chain management and responsibility, refer to the Altria website and the Corporate Responsibility Progress Report (http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html).

7.4.4. Environmental Sustainability

Manufacture of the New Product will not affect environmental sustainability. USSTC has an ongoing initiative to improve environmental sustainability across all facilities. One piece of infrastructure that supports this initiative is the EMS. (b) (4)

(b) (4). As a result of these efforts, USSTC expects its overall energy use to decrease over time.

(b) (4)

For more information on USSTC's environmental sustainability initiatives, refer to the Altria website and the Corporate Responsibility Progress Report (http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html).

(b) (4)

(b) (4)

However, the power supplier to these manufacturing facilities is Dominion Energy which has committed to meeting the renewable portfolio goals and standards set by policymakers in Virginia.[16] Dominion Energy has set a renewable energy goal in Virginia to achieve 15% renewable power by 2025.

8. MITIGATION MEASURES

(b) herewith provides the basis for a Finding of No Significant Impact for this environmental assessment of the New Product due to *de minimis* exposure. As such, no additional environmental protection measures, mitigation measures or alternative actions are necessary to address environmental impacts of the New Product.

[16] Refer to https://www.dominionenergy.com/renewables

9. ALTERNATIVES TO THE PROPOSED ACTION

Alternative A (No-action alternative): The no-action alternative is to not allow the marketing of the New Product in the United States.

Alternative B (Proposed action): Issuing a Finding of No Significant Impact due to the proposed action of granting an order finding that the New Product may be introduced or delivered for introduction into interstate commerce under Section 910(c)(1)(A)(i) of the FD&C Act.

The no-action alternative is not expected to significantly change the existing condition. Therefore, the difference between the environmental impacts of these two alternatives is negligible.

10. LIST OF PREPARERS

In accordance with 40 CFR 1502.17, this section includes a list of names and qualifications (including position/title, education, experience, and expertise) of individuals who were primarily responsible for preparing and reviewing this environmental assessment. No Agencies or persons besides subject matter experts within (b) and ALCS were consulted. However, feedback from FDA on prior submissions and examples of Environmental Assessments posted by FDA were considered in developing this assessment.

(b) (4)

Education: M.S. in Chemical Engineering; MBA

Years of Experience: > 25 years in environmental consulting

Qualifications: Environmental assessments and audits, environmental risk assessment, environmental compliance & assurance activities, air quality, and product stewardship and sustainability.

(b) (4)

Education: B.S. in Chemistry; M.S. in Environmental Engineering

Years of Experience: > 25 years in environmental management and regulatory activities

Qualifications: Environmental assessments, environmental risk assessment, environmental compliance & assurance activities, life cycle assessment, engineering design of pollution control measures, and product stewardship and sustainability.

(b) (4)

Education: B.S. in Mechanical Engineering

Years of Experience: 25 years in environmental management and regulatory activities

Qualifications: Environmental assessments and audits, environmental risk assessment, environmental compliance & assurance activities, air quality, Toxic Substances Control Act (TSCA) compliance, and product stewardship and sustainability.

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12. APPENDICES

As a final measure of substantiation for the minimal environmental risk associated with the use of the New Product, (b) has included the following Appendices.

Data summaries provide a brief summation of the available physico-chemical properties, toxicology and ecotoxicology data for the product ingredients and are included in Confidential Appendix 5-2-2. Data contained in the attached summaries are from publicly available compilations from sources including the USEPA and the European Chemicals Agency (ECHA). Specific references are noted as appropriate.

Additional information regarding the regulatory status of product ingredients are provided in Confidential Appendix 5-2-3 to further substantiate FDA's acceptance of these substances from an environmental perspective.

13. CERTIFICATION

(b) (4)

APPENDIX 5-2-2 – ENVIRONMENTAL ASSESSMENT
TRADE SECRET/CONFIDENTIAL COMMERCIAL INFORMATION RESPONSE
TO ADVICE/INFORMATION REQUEST FOR VERVE® CHEWS GREEN MINT

Data Summaries

Empty boxes in Data Summaries are intentionally left blank

Data contained in the attached summaries are from readily available compilations from sources including the US Environmental Protection Agency (EPA) and the European Chemicals Agency (ECHA). Specific references are noted as appropriate.

Ingredient ID#	Ingredient Name	Link
	(b) (4)	
1		Ingredient 1.pdf
2		Ingredient 2.pdf
3		Ingredient 3.pdf
4		Ingredient 4.pdf
5		Ingredient 5.pdf
7		Ingredient 7.pdf
8		Ingredient 8.pdf
9		Ingredient 9.pdf
11		Ingredient 11.pdf
12		Ingredient 12.pdf
14		Ingredient 14.pdf
16		Ingredient 16.pdf
17		Ingredient 17.pdf
18		Ingredient 18.pdf
19		Ingredient 19.pdf
20		Ingredient 20.pdf
21		Ingredient 21.pdf
24		Ingredient 24.pdf

(b) (4)

Ingredient ID#	Ingredient Name	Link
25	(b) (4)	Ingredient 25.pdf
26		Ingredient 26.pdf
28		Ingredient 28.pdf
29		Ingredient 29.pdf
30		Ingredient 30.pdf
32		Ingredient 32.pdf
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44		Ingredient 44.pdf
46		Ingredient 46.pdf
47		Ingredient 47.pdf
48		Ingredient 48.pdf
49		Ingredient 49.pdf

Ingredient ID#	Ingredient Name	Link
50	(b) (4)	Ingredient 50.pdf
52		Ingredient 52.pdf
53		Ingredient 53.pdf
55		Ingredient 55.pdf
56		Ingredient 56.pdf
57		Ingredient 57.pdf
60		Ingredient 60.pdf
61		Ingredient 61.pdf
62		Ingredient 62.pdf
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73		Ingredient 73.pdf
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75		Ingredient 75.pdf
76		Ingredient 76.pdf
78		Ingredient 78.pdf

(b) (4)

ENVIRONMENTAL ASSESSMENT
TRADE SECRET/CONFIDENTIAL COMMERCIAL INFORMATION
FOR THE PRODUCT IDENTIFIED AS VERVE® DISCS GREEN MINT

Memorandum

To:	Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC
From:	(b) (4)
Date:	May 24, 2018
Subject:	Environmental Assessment for the Premarket Tobacco Product Application for the Product Identified as VERVE® Discs Green Mint

This environmental assessment was prepared in accordance with 21 CFR 25.40, the Food and Drug Administration's (FDA's or Agency's) regulation implementing the National Environmental Policy Act of 1969. Under NEPA, "all applications or petitions requesting Agency action require the submission of an environmental assessment or a claim of categorical exclusion."[1]

(b) (4) respectfully submits the following environmental assessment in support of the *Premarket Tobacco Product Application (PMTA)* for the product identified as *VERVE® Discs Green Mint* (referred to throughout this assessment as the "New Product") pursuant to 21 CFR 25.20 because there is no applicable categorical exclusion for this type of application.

This environmental assessment was conducted in accordance with 21 CFR 25.40 and relevant aspects of FDA technical guidance documents including:

- *Environmental Considerations for Tobacco Product Applications Submitted to CTP, presented by Cristi Stark, M.S., Associate Director for Science Policy, Office of Science, CTP, FDA (August 2016);*
- *Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I (March 2001); and*
- *Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998).*

[1] 21 CFR 25.15(a)

This environmental assessment was prepared at the direction of Altria Client Services LLC (ALCS) on behalf of U.S. Smokeless Tobacco Company LLC (USSTC), a wholly owned subsidiary of Altria Group Inc. The potential aquatic, atmospheric, and terrestrial environmental impacts of FDA's approval of the PMTA and subsequent marketing of the New Product were considered using a conservative set of assumptions. The assessment identified no significant environmental risks, and a Finding of No Significant Impact by FDA is warranted for the environmental assessment of the New Product.

This memorandum contains trade secret and confidential commercial information that USSTC considers to be proprietary and highly sensitive, and which is protected from disclosure under the Food, Drug and Cosmetic Act §§ 301(j) and 906(c) (21 U.S.C. §§ 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. § 1905), the Freedom of Information Act (5 U.S.C. § 552), and FDA's implementing regulations, 21 CFR Part 20. If FDA receives a request for these records and tentatively determines that any portion of this submission is disclosable, USSTC requests that FDA provide notice and opportunity for USSTC to object to any disclosure in accordance with 21 CFR § 20.47 and 21 CFR § 20.61. USSTC reserves all of its legal rights to protect against public disclosure of its trade secret and confidential commercial information and to seek legal recourse against anyone who discloses such information without legal authorization.

1. DATE

May 24, 2018

2. NAME OF APPLICANT/SUBMITTER

Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC

3. ADDRESS

2325 Bells Road, Richmond, Virginia 23234

4. MANUFACTURER

U. S. Smokeless Tobacco Company LLC

5. DESCRIPTION OF PROPOSED ACTION

The proposed action is for FDA to issue a market authorization order under Section 910(c)(1)(A)(i) of the Food, Drug and Cosmetic Act (FD&C Act)[2] to introduce the New Product into interstate commerce. Through a PMTA for the New Product, USSTC is requesting approval from FDA to introduce the New Product into interstate commerce for commercial distribution in the United States. USSTC is including this environmental assessment with its submittal of the PMTA to FDA for the New Product.

6. IDENTIFICATION OF THE PRODUCT THAT IS THE SUBJECT OF THE PROPOSED ACTION

6.1. Type of Tobacco Product

Verve® discs are a chewable, non-dissolvable, tobacco-derived nicotine product (known as an oral nicotine-delivery product). The chewable form of the New Product has a soft, flexible texture.

6.2. Estimated Market Volumes

The following table presents the estimated first-year and fifth-year market volumes for the New Product. These estimated market volumes form the basis for the environmental exposure estimates provided in this assessment.

Table 1 – Estimated First-Year and Fifth-Year Market Volumes for the New Product

Name	Unit	New Product	
		First-Year Projected Market Volume	Fifth-Year Projected Market Volume
VERVE® Discs Green Mint	Tubes[3]	(b) (4)	
	Metric Tons		

6.3. Product Composition

The New Product contains tobacco-derived nicotine, (b) (4), non-tobacco cellulose fiber, flavorings, texture modifiers, binders and colorants.

[2] 21 U.S.C. 387j
[3] There are 16 discs in one tube.

6.3.1. *Product*

The formulation of the New Product is given in the following table. All values are reported in milligrams (mg).

Table 2 – Product Formulation

ID #[4]	CAS Number	Substance	Amount per Piece (mg)
1			(b)(4)
3			
6			
7			
9			
10			
15			
17			
22			
23			
26			
31			
36			
45			
50			
51			

[4] The ID# is a unique number for each ingredient; it corresponds to the list of ingredients in Confidential Appendix 5-4-2.

Table 2 – Product Formulation

ID #[1]	CAS Number	Substance	Amount per Piece (mg)
55			(b) (4)
58			
59			
60			
62			
66			
67			
68			
69			
70			
71			
74			
76			
77			
78			

6.3.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

6.3.2. Packaging

Packaging material for the New Product comprises the following components, with weight represented on a per product basis. The individual discs (16) are packaged in a vial which contains a vial, cap (lid), cap liner and a label. USSTC has designed all packaging materials

to meet FDA's standard for direct and indirect food additives set forth in Title 21 of the Code of Federal Regulations (CFR).

Table 3 – Characterization and Weight of Packaging Materials[5]

Packaging Component	Package Composition	Weight (grams)
Vial		(b) (4)
Cap		
Cap Liner		
Label		
Carton		
Case		

6.4. Location of Manufacture

The New Product will be manufactured at U.S. Smokeless Tobacco Products LLC, located at (b) (4) U.S. Smokeless Tobacco Products LLC is a business entity of United States Smokeless Tobacco Company (USSTC). The (b) (4) for the New Product.

[5] There are 16 discs per tube, 10 tubes per carton and 10 cartons per case.

6.5. Location of Use

USSTC intends to market the New Product to adult consumers throughout the United States.

6.6. Disposal Sites

The distribution of waste generated due to disposal of the New Product and/or packaging is expected to correspond to the pattern of product use. Disposed materials will either enter the recycling stream or be disposed of in municipal solid waste (MSW) landfills or as litter. Additional information is provided in Section 7.1.3 below.

7. ENVIRONMENTAL ISSUES

7.1. Introduction of the Product into the Environment

7.1.1. As a Result of Manufacture

No significant environmental impacts are anticipated as a result of manufacturing the New Product. (b) (4) .

(b) (4)

(b) (4)

According to the U.S. Environmental Protection Agency (USEPA)'s most recent National Biennial Report data (https://rcrainfo.epa.gov/rcrainfoweb/action/modules/br/summary/view), 33,646,921 tons of hazardous wastes were generated across the United States in 2015. Of this amount, over 2,688,613 tons were incinerated or used (combusted) for energy recovery. Assuming the entire production volume is disposed of by the manufacturing facility, the New Product is expected to generate up to (b) (4) of hazardous waste per year.[6] This represents up to (b) (4) of the total hazardous waste in the country and up to (b) (4) of the total hazardous waste treated by incineration or used (combusted) for energy recovery in the country. Thus, the contribution of the New Product to total hazardous waste generated and treated by incineration (or energy recovery) annually in the United States is miniscule. Therefore, additional resources (e.g., new incineration or similar treatment facilities, etc.) will not be required for disposal of the New Product.

Section 7.1.3 addresses the solid waste generation expected to result from use of the New Product. The New Product following use by consumers is an exempt household hazardous waste and is not subject to regulation as hazardous waste.

No significant environmental impacts are anticipated as a result of manufacturing the New Product.

7.1.2. As a Result of Use

The aquatic environment is the primary compartment of concern for environmental releases resulting from use of the New Product. The New Product is used orally. Therefore, exposure to the terrestrial and atmospheric environments is not anticipated.

7.1.2.1. Aquatic

7.1.2.1.1. Product

The New Product ingredients are expected to be released primarily to the aquatic environment via excretion as a result of product use. To quantify the anticipated amount of

[6] Maximum US tons of MSW per year = A*B*C; where A = Maximum Annual Shipping Quantity between 1st Year and 5th Year (g), B = Weight of product (g), C = 1 / 907,185 g/US Ton (Conversion from g to US Tons)

each chemical substance contained in the New Product to the aquatic environment, (b) (4) calculated the annual load (kilograms per year, or kg/yr) and the aquatic expected introduction concentration (EIC) (micrograms per liter, or µg/L). (b) (4) applied the approach FDA established for human drugs and biologics to calculate the aquatic EIC as follows:

EIC-aquatic (ppb or µg/L) =A * B * C * D, where

A=kg/yr produced,

B=1/1.071x10^{11} L/day entering POTW (Publicly Owned Treatment Works facility)

(Source: Clean Watersheds Needs Survey (NWNS) 2012 Data and Reports, Detailed Listing of Waste Water Treatment Plant Flows for the Nation accessible at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:4:::::RP::),

C=year/365,

D=10^{9} µg/kg

In calculating the aquatic EIC values, (b) (4) maintained the following conservative assumptions that were established in FDA guidance:[7]

- The kg/year produced is based on the highest quantity expected to be produced for direct use in any of the next five years;
- All product produced in a year is used and enters the POTW system [The ingredients are absorbed by the human body during use and 100% of the ingredients are then excreted to sanitary sewer and to treatment within the POTW];[8]
- New Product usage occurs throughout the United States in proportion to the population and amount of wastewater generated;
- No dilution occurs in receiving waters; and
- There is no metabolism.

The results of these calculations were compared to FDA's established concentration of concern (1 µg/L or ppb). As described in its 2001 technical guidance document, *Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I*, FDA considers this value to be below the level shown to have adverse effects in aquatic ecotoxicity studies with human drugs. This was deemed appropriate for

[7] Guidance for Industry: Environmental Assessment of Drug and Biologics Applications (July 1998)

[8] (b) (4)

the current assessment as No Observed Effect Concentration (NOEC) values for each substance, where available, are greater than 1 µg/L or ppb.

A brief summary of publicly available fate and effects data for each ingredient of the New Product is provided in Confidential Appendix 5-4-2 for reference.

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
		(b)(4)

[9] (annual production forecast)x(relative amount in formulation)

[10] EI Caquatic (ppb or µg/L)=A*B*C*D; where A=kg/yr produced, B=1/1.071x10[11] L/day entering POTW (Source: Clean Watersheds Needs Survey (NWNS) 2012 Data and Reports, Detailed Listing of Waste Water Treatment Plant Flows for the Nation accessible at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:4:::RP::), C=year/365, D=10[9] µg/kg

Table 4 - Aquatic Annual Load and EIC for the New Product

Substance	Annual Load (kg/yr)[9]	Aquatic EIC (µg/L)[10]
		(b) (4)

(b) (4) noted that in every case, the aquatic EIC is (b) (4) at the point of entry into the aquatic environment, which is below the relevant concentration of concern identified in FDA guidance.

7.1.2.1.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

In Table 4, (b) (4) noted that the EIC calculated for nicotine is (b) (4) at the point of entry into the aquatic environment and therefore below FDA's established concentration of concern. Nonetheless, fate and effects data for nicotine are discussed in detail in Sections 7.2 and 7.3 of this assessment.

7.1.2.1.2. Packaging

Packaging is not intended or expected to release chemical substances during use. Releases as a result of disposal are discussed in Section 7.1.3 of this assessment.

7.1.3. As a Result of Disposal

Following use by consumers, the New Product is an exempt household waste and is not subject to regulation as hazardous waste. The New Product will be disposed of in MSW landfills or as litter. The associated packaging materials will either be recycled or be disposed of in MSW landfills or as litter. The New Product will be disposed of in the same way as other commercially marketed consumer chewable products (e.g., chewing gums or chewable tablets). The distribution of waste generated due to disposal of the New Product and packaging is expected to correspond to the pattern of product use throughout the United States.

Disposal following use of the New Product is not expected to require additional resources for waste disposal. The terrestrial environment is the primary compartment of concern for environmental releases of the New Product as a result of disposal. Any release to the aquatic environment as a result of disposal is addressed by the calculations conducted in Section 7.1.2.

7.1.3.1. Disposal of the Product Following Use

According to the U.S. Environmental Protection Agency (USEPA) document, *Advancing Sustainable Materials Management: 2014 Fact Sheet Assessing Trends in Material Generation, Recycling, Composting, Combustion with Energy Recovery and Landfilling in the United States*, 258 million tons of MSW were generated across the United States in 2014. Of this, over 89

million tons (34.6%) were recycled and composted, more than 136 million tons (52.6%) were discarded in a landfill, and more than 33 million tons (12.8%) were combusted with energy recovery (USEPA, 2016a). Chewable nicotine products (oral nicotine-delivery products) are not expected to be recycled.

Assuming the entire production volume is disposed of in a landfill, the New Product is expected to generate up to (b) (4) of MSW per year.[11] This represents up to (b) (4) of the total MSW in the country and up to (b) (4) of MSW that is disposed of in landfills in the country. Thus, the contribution of the New Product to total MSW disposed annually in the United States is miniscule. Therefore, additional resources (e.g., new landfills, recycling centers, etc.) will not be required for disposal following use of the New Product.

Proper disposal will be to landfill and not directly to the terrestrial environment. Disposal to MSW landfills will not result in adverse effects to the environment based on landfill design and regulatory requirements. Disposed waste streams within a landfill are prevented from entering the environment and ultimately landfill leachate is treated and/or sent to POTWs for effective treatment.

Disposal following use of the New Product is not expected to result in new or additional compounds emitted to the environment. USSTC anticipates the New Product will be disposed of following use in the same way as other commercially marketed consumer chewable products (e.g., chewing gums or chewable tablets). The distribution of waste generated due to disposal of the New Product is expected to correspond to the same pattern of product use. No new or additional environmental effects, as defined within 40 CFR 1508.8, are anticipated. However, improper disposal may occur. The calculations provided in Section 7.1.3.2 conservatively address product that is inappropriately disposed of directly to the environment.

7.1.3.2. Terrestrial

7.1.3.2.1. Product

Introduction of the New Product to the terrestrial environment was calculated as surface density. Absent guidance from FDA on the appropriate duration to be used for this calculation and because it is conservatively assumed there is no metabolism or depletion in the environment, a timeframe had to be selected. Therefore, the terrestrial surface density of each ingredient was calculated on a per day basis.

[11] Maximum US tons of MSW per year = A*B*C; where A = Maximum Annual Shipping Quantity between 1st Year and 5th Year (g), B = Weight of product (g), C = 1 / 907,185 g/US Ton (Conversion from g to US Tons)

The daily terrestrial surface density values are presented in following table as the production tonnage distributed across the surface area of the United States per day (nanograms per square meter per day, or ng/m^2 per day). These values were based on the very conservative assumptions that the entire production volume was introduced to commerce and that the New Product is released to the terrestrial environment in its complete and unused state. The calculation is shown in the footnote for the table.

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)[12]
	(b) (4)

[12] Daily Surface Density (ng/m^2 per day) = A*B*C*D*E; where A = mg/yr produced, B = 1/9.158x10^6 km^2 surface area of the United States, C = year/365 days, D = 10^6 km^2/m^2, E = 10^6 ng/mg

Table 5 – Daily Terrestrial Surface Density Values for the New Product

Substance	Terrestrial Surface Density (ng/m^2 per day)[1]
(b) (4)	

The daily terrestrial surface density values presented as a production tonnage distributed across the surface area of the United States are (b) (4) ng/m^2 per day as determined using the calculations shown in the footnote in the table above. The values are so small that

exposure to the New Product in the terrestrial environment as described here would not have a significant effect.

Based on the mass of non-nicotine ingredients shown in Table 2 and publicly available environmental fate and effects data, a single used or unused disc that is improperly disposed is not expected to cause localized effects to the terrestrial environment. Adverse effects are highly unlikely because improper disposal of discs should occur only on rare occasions and the non-nicotine ingredients are expected to exhibit a low order of environmental toxicity.

7.1.3.2.1.1. Nicotine

The maximum nicotine content of the New Product is 1.5 mg per piece.

The daily terrestrial surface density value for nicotine as the production tonnage distributed across the surface area of the United States per day (ng/m^2 per day)[13] is (b) (4) ng/m^2 per day. This was based on the very conservative assumptions that the entire production volume was introduced to commerce and that the New Product is released to the terrestrial environment in its complete and unused state.

(b) (4)

[13] Daily Surface Density (ng/m^2 per day) = A*B*C*D*E; where A = mg/yr produced, B = 1/9.158x10^6 km^2 surface area of the United States, C = year/365, D = 10^{-6} km^2/m^2, E = 10^6 ng/mg

7.1.3.3. Disposal of Packaging Following Use

The New Product's packaging is expected to be disposed of following use in the same way as packaging from other commercially marketed consumer chewable products. The distribution of waste generated due to disposal of packaging is expected to correspond to the same pattern of product use.

According to the USEPA document, *Advancing Sustainable Materials Management: 2014 Fact Sheet Assessing Trends in Material Generation, Recycling, Composting, Combustion with Energy Recovery and Landfilling in the United States*, 258 million tons of MSW were generated across the United States in 2014. Of this, over 89 million tons (34.6%) were recycled and composted, more than 136 million tons (52.6%) were discarded in a landfill, and more than 33 million tons (12.8%) were combusted with energy recovery (USEPA, 2016a). Assuming all of the New Product packaging is disposed of to landfill, packaging from the New Product is expected to generate up to (b) (4) of MSW per year[14]. This represents up to (b) (4) of the total MSW in the country and up to (b) (4) of MSW that is disposed of in landfills in the country. Thus, the contribution of the New Product's packaging to total MSW disposed annually in the United States is miniscule. Therefore, disposal of the New Product's packaging following use of the New Product is not expected to require additional resources (e.g., new landfills, recycling centers, etc.) for waste disposal.

Disposal of packaging following use of the New Product is not expected to result in new or additional compounds emitted to the environment. The materials used in the packaging of the New Product (b) (4) are common packaging materials used for consumer products in general. Proper disposal will be to landfill and not directly to the terrestrial environment. Disposal to MSW landfills will not result in adverse effects to the environment based on landfill design and regulatory requirements. The same or similar compounds and types of emissions are anticipated from disposal of the packaging of the New Product as those associated with disposal of the packaging of other consumer chewable products or consumer products in general. Thus, no new or additional environmental effects, as defined within 40 CFR 1508.8, are anticipated.

7.2. Fate of Product Released into the Environment

Due to its ecotoxicological relevance, we discuss the fate of nicotine released into the environment in this Section even though nicotine is below concentrations of concern based on the exposure assessments within this environmental assessment.

[14] (b) (4)

7.2.1. Nicotine

Quantitative Structure Activity Relationships (QSARs) have been used to describe the physical-chemical properties of nicotine and to provide predicted aquatic toxicity values to support the use of nicotine as a marker compound. Acceptable QSARs are not available to predict toxicity to terrestrial organisms. All QSAR predictions were determined using the USEPA's EpiWeb 4.1.[15]

7.2.1.1. Physical Chemical Properties

The physical-chemical properties of pure nicotine (CAS 54-11-5) and its metabolites are presented in the following table. Nicotine's physical-chemical properties can be used to assess the fate of nicotine introduced into the environment.

Nicotine introduced into water will stay mainly in water and will not readily partition to air based on its low Henry's Law Constant ($3x10^{-9}$ atmospheres – cubic meters per mole or atm-m^3/mole) and negative air/water partitioning coefficient (K_{aw} = -6.910) (USEPA, 2016b). Nicotine in water should not bioaccumulate or bioconcentrate in aquatic organisms (measured log K_{ow} = 1.17) (Hansch, Hoekman, Leo, Zhang, & Li, 1995). The predicted bioconcentration factor (log BCF) for nicotine of 0.440 supports this conclusion.

Nicotine introduced into the soil can volatilize to air based on the vapor pressure of 0.032 mm Hg (Boublik, 1984). However, the extent to which it actually volatilizes will depend on its sorption. The log K_{oc} predicted at neutral pH is 2.720 and indicates that nicotine in soil has moderate mobility. The mobility of nicotine, a weak acid (pK_a 8.5), is pH dependent and will increase at alkaline pH. Because nicotine is highly soluble (predicted solubility $1.000x10^6$ milligrams per liter, or mg/L) and has a negative K_{aw}, it will most likely partition to soil pore-water rather than air.

[15] The EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical/chemical property and environmental fate estimation programs developed by the USEPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). EPI Suite™ uses a single input to run the following estimation programs: KOWWIN™, AOPWIN™, HENRYWIN™, MPBPWIN™, BIOWIN™, BioHCwin, KOCWIN™, WSKOWWIN™, WATERNT™, BCFBAF™, HYDROWIN™, KOAWIN and AEROWIN™, and the fate models WVOLWIN™, STPWIN™ and LEV3EPI™. ECOSAR™, which estimates ecotoxicity, is also included in EPI Suite™ (USEPA, 2016b).

Table 6a – Predicted Physical-Chemical Properties of Nicotine and Related Compounds

CAS	IUPAC Name	Water Solubility	Vapour Pressure	Henry's Law Constant	Log K_{ow}	log K_{oc}	Log K_{oa}
		mg/L	mm Hg	atm-m^3/mol			
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	1 000E+06	3 200E-02	3 000E-09	9 980E-01	2 720E+00	8 080E+00
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	9 990E+05	3 810E-04	3 330E-12	3 400E-01	2 110E+00	8 038E+00
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	1 000E+06	2 160E-07	5 200E-13	-1 200E+00	1 010E+00	9 190E+00
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	1 000E+06	1 660E-05	1 520E-12	-3 000E-01	2 100E+00	9 900E+00
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	6 030E+05	5 120E-04	1 970E-10	3 210E-01	3 200E+00	8 480E+00
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	5 040E+03	5 130E-07	3 000E-14	6 860E-01	2 190E+00	1 260E+01
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	3 060E+05	6 040E-05	1 970E-10	5 970E-01	3 470E+00	8 690E+00
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	1 960E+05	6 680E-05	8 580E-11	8 120E-01	3 470E+00	8 850E+00

Table 6b – Predicted Physical-Chemical Properties of Nicotine and Related Compounds

CAS	IUPAC Name	Log K_{aw}	BCF	Photo-chemical half-life	Half-life in water	Half-life in soil
				hrs	days	days
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	-6.910E+00	4.400E-01	1.410E+00	3.750E+01	7.500E+01
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	-8.040E+00	5.000E-01	4.900E+00	3.750E+01	7.500E+01
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	-1.067E+01	5.000E-01	4.300E+00	3.750E+01	7.500E+01
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	-1.027E+01	5.000E-01	7.990E+00	6.000E+01	1.200E+02
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	-8.160E+00	5.000E-01	5.400E+00	6.000E+01	1.200E+02
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	-1.191E+01	5.000E-01	4.200E+00	6.000E+01	1.200E+02
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	-8.090E+00	5.000E-01	1.430E+00	6.000E+01	1.200E+02
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	-8.030E+00	5.000E-01	3.380E+00	6.000E+01	1.200E+02

7.2.1.2. Degradation

Nicotine lacks hydrolyzable groups and, therefore, will not undergo abiotic hydrolysis. However, nicotine has the potential to undergo direct photolysis. Nicotine's electronic absorption spectrum shows an intense absorption band at 260-262 nanometers (nm) with some absorption above 290 nm (within the spectrum of energies provided by sunlight) (Sangster & Stuart, 1965). The predicted photochemical half-life for nicotine in air is 1.4 hours. Nicotine can also degrade in surface waters via indirect photolysis by naturally occurring photosensitizers such as dissolved organic matter and hydroxyl radicals. Thus, indirect photolysis can play an important role in the degradation of nicotine.

Biotransformation of nicotine in soils and water-sediment systems has been documented. In soils, nicotine is oxidized by the bacteria *Arthrobacter oxydans* (now known as *Arthrobacter nicotinovarans*). The relative amounts and conditions of biotransformation will vary with soil and bacterial populations. The nature of the transformations in soil is not as well defined as those in animals. It has been demonstrated *in vitro* that the first metabolite of nicotine is 6-hydroxynicotine, which further breaks down to 6-hydroxypseudonicotine

(oxynicotine) and other compounds. Cotinine, which is a major oxidation product of nicotine in the liver, has not been reported to form in soils; however, microorganisms isolated from soils in tobacco fields are capable of degrading nicotine to cotinine in solution (Wang et al., 2012).

Nicotine and its metabolite, cotinine, have been reported to biotransform in sediments (Bradley, Barber, Kolpin, McMahon, & Chapelle, 2007). Under oxidizing conditions nicotine and cotinine degrade completely to CO_2 within 72 days. Under anoxic conditions the biotransformation of nicotine and cotinine is slower. EpiWeb 4.1 predicts half-lives of 37.5 days for nicotine and cotinine in water and 75 days in soil under aerobic conditions.

Data on the transformation products or metabolites of nicotine are very limited. In order to have a common frame of reference, we compared the predicted values for nicotine to the predicted values for the metabolites. Predicted physical-chemical properties of nicotine metabolites and transformation products compare to those of nicotine as follows. Predicted log K_{ow} values range from -1.200 to 0.998. Predicted log K_{oc} ranges from 1.010 to 3.470. Predicted water solubilities range from 5.040×10^3 mg/L to 1.000×10^6 mg/L with nicotine being among the more soluble substances. Predicted Henry's Law Constants range from 3.000×10^{-14} atm-m^3/mole to 3.000×10^{-9} atm-m^3/mole for nicotine and related compounds. Predicted photochemical half-lives range from 1.410 to 7.990 days for nicotine and related compounds. Predicted half-lives in water are all less than 60 days and half-lives in soil are predicted to be less than 120 days. Relative to its metabolites, nicotine is more water soluble and more volatile, and degrades somewhat more quickly. Its behavior was deemed similar enough to that of its metabolites to serve as an appropriate surrogate in the environmental assessment.

7.3. Environmental Effects of Product Released into the Environment

Due to its ecotoxicological relevance, we discuss the effects of nicotine released into the environment in this Section even though nicotine is below concentrations of concern based on the exposure assessments within this environmental assessment.

7.3.1. Nicotine

QSAR predictions in Table 7 were used here as a basis of comparison among nicotine and related compounds and should be taken as qualitative rather than quantitatively definitive. Equations for different classes of compounds used to develop the ECOSAR model within OECD Toolbox V2.38 (OECD, 2012) are of differing reliabilities depending on the dataset used to develop the equation.

Table 7 - Acute Aquatic Toxicity of Nicotine and Related Compounds

CAS	IUPAC Name	Algal 96-EC_{50}	Daphnia 48-hr - EC_{50}	Fish 96-hr LC_{50}
		mg/L	mg/L	mg/L
54-11-5	3-[(2S)-1-Methyl-2-pyrrolidinyl]pyridine	44.70	0.20	4.86
486-56-6	(5S)-1-Methyl-5-(3-pyridinyl)-2-pyrrolidinone	17.80	1.92E+03	8.11E+02
34834-67-8	(5S)-3-Hydroxy-1-methyl-5-(3-pyridinyl)-2-pyrrolidinone	176.00	5.35E+04	1.11E+04
171140-40-8	5-(3-Pyridinyl)-2-pyrrolidinone	22.20	2.75E+03	1.06E+03
16543-55-8	3-[(2S)-1-Nitroso-2-pyrrolidinyl]pyridine	131.00	0.22	8.66
127686-49-1	{Nitroso[4-oxo-4-(3-pyridinyl)butyl]amino}methyl acetate	42.50	38.00	372.00
119738-26-0	(2S)-1-Nitroso-1,2,3,6-tetrahydro-2,3'-bipyridine	93.30	0.23	7.57
1133-64-8	3-[(2S)-1-Nitroso-2-piperidinyl]pyridine	69.00	0.24	6.55

Predicted algal 96-hr EC_{50} values range from 17.8 mg/L to 176 mg/L. The predicted EC_{50} for nicotine (CAS 54-11-5) is 44.7 mg/L. While not predicted to be the most toxic compound, nicotine toxicity is within a factor of 2 of the most toxic compounds and likely not significantly different (i.e., within the confidence limits of the prediction). Measured 96-hr EC_{50} values for the toxicity of nicotine to the alga *Selenastrum capricornutum* were 72.9 mg/L for growth and 115 mg/L for biomass (Seckar, et al., 2008). The predicted EC_{50} values for nicotine were lower than the measured values but within a factor of 2.

The predicted 48-hr EC_{50} of nicotine to *Daphnia* is 0.2 mg/L. Predicted toxicity values for the nicotine metabolites range from 0.22 mg/L to 5,350 mg/L. The measured EC_{50} value for *Daphnia pulex* is 0.24 mg/L (Savino & Tanabe, 1989).

The predicted fish 96-hr LC_{50} for nicotine is 4.86 mg/L. The predicted LC_{50} values for metabolites of nicotine range from 6.55 to 11,000 mg/L. Measured LC_{50} values for nicotine toxicity to *Oncorhynchus mykiss* larvae are 4 mg/L (96 hrs), 5 mg/L for fry (60 days), and 6 mg/L for fry (21-31 days).

Terrestrial toxicity data for invertebrates were of limited availability. Because nicotine has a history of use as a pesticide, it is expected that terrestrial invertebrates will be very sensitive to nicotine. Rizvi et al. reported that the 24-hr LD_{50} of nicotine dust was 7.2 micrograms (µg)/nymph for *Dysdercus koenigii (Fabr.)* (Rizvi, Ahmed, & Naqvi, 2012). Additional toxicity data are included on dermal toxicity to the brown tree snake, oral toxicity to rats, and dermal toxicity to rabbits. Terrestrial toxicity to the brown tree snake (*Boiga irregularis*) is reported as 40 milligrams per kilogram (mg/kg) dermally, a dose that killed 100% of snakes (Brooks, Savarie, & Johnston, 1998). The oral LD_{50} dose for nicotine in rats is 50 mg/kg to 60 mg/kg (Klaasen, Amdur, & Doull, 1995). The dermal LD_{50} in rabbits is reported as 140 mg/kg (Lewis, 1996).

7.4. Use of Resources and Energy

Based on the estimated maximum annual market volume of the New Product (from the five-year projected market volume), the use of resources and energy due to the proposed action is expected to be negligible.

7.4.1. Energy Consumption / Greenhouse Gas Emissions

The New Product manufacturing process is (b) (4) The process does not emit greenhouse gas (GHG) pollutants. Energy consumption due to warehousing and distribution is expected to be similar to other consumer products of similar size.

Additional information on energy and resource sustainability efforts are described in Section 7.4.4.

7.4.2. Compliance with ESA and CITES

No critical habitat is affected from materials or ingredients used to manufacture the New Product.

No adverse effects are expected on a species or the critical habitat of a species identified under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) due to the manufacture or marketing of the New Product.

USSTC does not anticipate that any critical habitat or endangered or threatened species will be affected from production of the New Product, or from materials or ingredients used to manufacture the New Product. Altria and USSTC's supply contracts and supplier code of conduct standards support compliance with applicable laws (refer to Section 7.4.4). For more information on supply chain management and responsibility, refer to the Altria website and the Corporate Responsibility Progress Report available at http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html.

The manufacturing facilities are not within or in close proximity to a critical habitat of a threatened or endangered species. USSTC does not expect the manufacture and commercial introduction of the New Product to affect a critical habitat or threaten the existence of listed species or destroy or adversely modify any designated critical habitat for that species. This

is based on a review of critical habitat maps (https://databasin.org/datasets/d579d87eb54f4374a77ea53e7ef66449) created by the U.S. Fish and Wildlife Service (US FWS), which show no critical habitat within close proximity to the manufacturing facilities.

The US FWS's list of species by county (https://www.fws.gov/endangered/) shows that Chesterfield County and Henrico County, Virginia may have one endangered species (Clams – James spinymussel (*Pleurobema collina*)) and three threatened species (Mammals – Northern Long-Eared Bat (*Myotis septentrionalis*; Flowering Plants – Sensitive joint-vetch (*Aeschynomene virginica*), Swamp pink (*Helonias bullata*)). However, these threatened or endangered species are not known to be in the vicinity of the manufacturing facility.

(b) (4)

As described in Section 7.1.1, waste generated as a result of manufacturing the New Product will be considered a hazardous waste (nicotine-containing material) and will be disposed of at waste incineration facilities or will be recycled via a nicotine reclamation facility. As described in Section 7.1.3, the used New Product will be disposed of in the same way as other commercially marketed chewable products. The distribution of waste generated due to disposal of the New Product and packaging is expected to correspond to the pattern of product use in the United States.

(b) (4)

7.4.3. Compliance with Federal, State and Local Environmental Regulations

The (b) (4), where the New Product will be manufactured, comply with the Clean Air Act (CAA), Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). Manufacture of the New Product will not result in changes in compliance with relevant federal, state and local environmental regulations. The facilities' compliance with the CAA, CWA, the RCRA, and other environmental regulations can be assessed on the USEPA's Enforcement and Compliance History Online (ECHO) website.

USSTC maintains an effective Environmental Management System (EMS) which is designed and implemented to integrate environmental programs (including compliance and sustainability) into business operations. Key components of the EMS include: personnel, policy, directives, guidance and training, data management and assessments.

(b) (4)

Regarding waste management, USSTC seeks to (b) (4)

The (b) (4)

(b) (4)

USSTC's long-term contracts with material suppliers, and the purchase order terms and conditions applicable to suppliers without long-term contracts, contain provisions that require compliance with all applicable laws and regulations. Altria's Supplier Code of Conduct also addresses compliance with applicable laws, regulations, and standards, which includes environmental compliance. (b) (4) For more information on supply chain management and responsibility, refer to the Altria website and the Corporate Responsibility Progress Report (http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html).

7.4.4. Environmental Sustainability

Manufacture of the New Product will not affect environmental sustainability. USSTC has an ongoing initiative to improve environmental sustainability across all facilities. One piece of infrastructure that supports this initiative is the EMS. (b) (4) As a result of these efforts, USSTC expects its overall energy use to decrease over time.

(b) (4) . For more information on USSTC's environmental sustainability initiatives, refer to the Altria website and the Corporate Responsibility Progress Report (http://www.altria.com/Interactive/2017CRReport/files/assets/basic-html/page-1.html).

(b) (4)

(b) (4)

(b) (4)

However, the power supplier to these manufacturing facilities is Dominion Energy which has committed to meeting the renewable portfolio goals and standards set by policymakers in Virginia.[16] Dominion Energy has set a renewable energy goal in Virginia to achieve 15% renewable power by 2025.

8. MITIGATION MEASURES

(b) (4) herewith provides the basis for a Finding of No Significant Impact for this environmental assessment of the New Product due to *de minimis* exposure. As such, no additional environmental protection measures, mitigation measures or alternative actions are necessary to address environmental impacts of the New Product.

9. ALTERNATIVES TO THE PROPOSED ACTION

Alternative A (No-action alternative): The no-action alternative is to not allow the marketing of the New Product in the United States.

Alternative B (Proposed action): Issuing a Finding of No Significant Impact due to the proposed action of granting an order finding that the New Product may be introduced or delivered for introduction into interstate commerce under Section 910(c)(1)(A)(i) of the FD&C Act.

The no-action alternative is not expected to significantly change the existing condition. Therefore, the difference between the environmental impacts of these two alternatives is negligible.

10. LIST OF PREPARERS

In accordance with 40 CFR 1502.17, this section includes a list of names and qualifications (including position/title, education, experience, and expertise) of individuals who were primarily responsible for preparing and reviewing this environmental assessment. No Agencies or persons besides subject matter experts within (b) and ALCS were consulted.

[16] Refer to https://www.dominionenergy.com/renewables

However, feedback from FDA on prior submissions and examples of Environmental Assessments posted by FDA were considered in developing this assessment.

(b) (4)

Education: M.S. in Chemical Engineering; MBA

Years of Experience: > 25 years in environmental consulting

Qualifications: Environmental assessments and audits, environmental risk assessment, environmental compliance & assurance activities, air quality, and product stewardship and sustainability.

(b) (4)

Education: B.S. in Chemistry; M.S. in Environmental Engineering

Years of Experience: > 25 years in environmental management and regulatory activities

Qualifications: Environmental assessments, environmental risk assessment, environmental compliance & assurance activities, life cycle assessment, engineering design of pollution control measures, and product stewardship and sustainability.

(b) (4)

Education: B.S. in Mechanical Engineering

Years of Experience: 25 years in environmental management and regulatory activities

Qualifications: Environmental assessments and audits, environmental risk assessment, environmental compliance & assurance activities, air quality, Toxic Substances Control Act (TSCA) compliance, and product stewardship and sustainability.

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12. APPENDICES

As a final measure of substantiation for the minimal environmental risk associated with the use of the New Product, (b) (4) has included the following Appendices.

Data summaries provide a brief summation of the available physico-chemical properties, toxicology and ecotoxicology data for the product ingredients and are included in Confidential Appendix 5-4-2. Data contained in the attached summaries are from publicly available compilations from sources including the USEPA and the European Chemicals Agency (ECHA). Specific references are noted as appropriate.

Additional information regarding the regulatory status of product ingredients are provided in Confidential Appendix 5-4-3 to further substantiate FDA's acceptance of these substances from an environmental perspective.

13. CERTIFICATION

(b) (4)

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APPENDIX 5-4-2 – ENVIRONMENTAL ASSESSMENT
TRADE SECRET/CONFIDENTIAL COMMERCIAL INFORMATION RESPONSE
TO ADVICE/INFORMATION REQUEST FOR VERVE® DISCS GREEN MINT

Data Summaries

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Data contained in the attached summaries are from readily available compilations from sources including the US Environmental Protection Agency (EPA) and the European Chemicals Agency (ECHA). Specific references are noted as appropriate.

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