U.S. Food & Drug Administration
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Silver Spring, MD 20993
www.fda.gov

PMTA Scientific Review: Technical Project Lead (TPL)

New Tobacco Products Subject of this Review[1]	
STN	PM0000470-PM0000473
Common Attributes	
Submission Date	July 23, 2018
Receipt Date	July 23, 2018
Applicant	U.S. Smokeless Tobacco Company LLC
Product manufacturer	U.S. Smokeless Tobacco Company LLC
Application type	Standard
Product category	Other
Product subcategory	Other
Cross-Referenced Submission	
All new tobacco products	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All new tobacco products	None
Recommendation	
Issue Marketing Order Letters	

DISCIPLINES REVIEWED	Primary Reviewers	DATE OF REVIEW
Behavioral and Clinical Pharmacology	**Babita Das, Kia Jackson**	**June 26, 2020**
Chemistry	**Lida Oum**	**July 14, 2020**
Environmental Science	**Ronald Edwards**	**June 25, 2020**
Engineering	**Rashele Moore**	**June 26, 2020**
Epidemiology	**Carol Christensen**	**June 25, 2020**
Medical	**Theresa Watkins-Bryant**	**June 29, 2020**
Microbiology	**David Craft**	**June 26, 2020**
OCE – DEM (BIMO)	**Rachel Mohseni**	**June 26, 2020**
OCE – DEM (Laboratory)	**Ronald Yi**	**June 29, 2020**
OCE – DEM (Manufacturing)	**Ronald Yi**	**June 29, 2020**
OCE – DPAL	**Victoria Grabhorn**	**June 29, 2020**
OHCE	**Emily Talbert**	**October 8, 2021**
Social Science	**Jen Bernat**	**June 25, 2020**
Statistics	**Christopher Ellison**	**June 29, 2020**
Toxicology	**Erica Clark**	**July 1, 2020**

1. [1] Product details, amendments, and dates provided in Appendix B. STN = submission tracking number(s).

Technical Project Lead (TPL):

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Sheila Healy, Ph.D.
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☒ Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

Signatory:

Matthew R. Holman, Ph.D.
Director, Office of Science

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1. EXECUTIVE SUMMARY

On July 23, 2018, the Food and Drug Administration (FDA) received four PMTAs from Altria Client Services LLC (ALCS), submitted on behalf of U.S. Smokeless Tobacco Company LLC (USSTC). The applicant is seeking market authorizations for four oral tobacco products under the brand name of VERVE®. The four products are mint products, two disc and two chew products, with the names VERVE® Discs Blue Mint, VERVE® Discs Green Mint, VERVE® Chews Blue Mint, and VERVE® Chews Green Mint. FDA issued acknowledgement letters to the applicant on August 22, 2018. These products are categorized as "other."

On September 19, 2018, FDA received the applicant's response (PM0000477) to information requested during a teleconference held on September 5, 2018. FDA issued a Filing letter on February 8, 2019. On February 14, 2019, FDA received an unsolicited amendment containing updates to the PMTAs (PM0000500). FDA issued an Information Request letter on February 20, 2019, detailing the number of samples requested to conduct independent testing of the new tobacco products that are the subject of the PMTAs. FDA issued an Inspection Request letter on February 21, 2019. On February 27, 2019, FDA received the applicant's response to the Information Request letter (PM0000504). On March 7, 2019, FDA received the applicant's response to the Inspection Request letter (PM0000505). On May 8, 2019, FDA received an unsolicited amendment containing corrections to validation reports previously submitted to FDA (PM0000512).

The VERVE® products are novel oral tobacco products that do not contain cut, ground, powdered, or leaf tobacco. All four products are used by the consumer by placing them in the mouth and chewing them, with the product being discarded, rather than swallowed, once the user is finished with the product. The Discs and Chews differ in part by the texture of the products. While both the Discs and the Chews are flexible, the Discs have a firm texture and the Chews have a soft texture. The applicant claims the products are intended for adult tobacco consumers interested in an oral tobacco product. They also note that the products have significantly lower levels of harmful and potentially harmful constituents (HPHCs) than smokeless tobacco products as well as cigarette smoke; the applicant states that, should an adult smoker switch totally to a VERVE® product, the consumer would be exposed to substantially lower HPHC levels, or even eliminate exposure to some HPHCs. The applicant also claims that the VERVE® products are not appealing to nonusers.

A new tobacco product, including a tobacco product modified in any way ("including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient"), that was not commercially marketed in the United States as of February 15, 2007 (section 910(a)(1)(B) of the Federal Food, Drug, and Cosmetics Act (FD&C Act) generally requires premarket authorization from FDA (section910(a)(2)(A) of the FD&C Act). A PMTA must be submitted to FDA under section 910(b) of the FD&C Act, and a marketing authorization order must be received from FDA under section 910(c)(1)(A)(i) prior to marketing any new tobacco product, unless FDA has found that the new tobacco product is substantially equivalent to a tobacco product commercially marketed in the U.S. as of February 15, 2007 (see section 910(a)(2)(A)(i) of the FD&C Act) or is exempt from a substantial equivalence determination pursuant to regulation (see section 910(a)(2)(A)(ii) of the FD&C Act).

FDA will deny a PMTA and issue a no marketing authorization order stating that the product may not be introduced or delivered for introduction into interstate commerce under section 910(c)(1)(A)(ii) where FDA finds that:

- there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health;
- the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to the manufacturing requirements of section 906(e) (21 U.S.C. 387f(e));
- based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or
- such tobacco product is not shown to conform in all respects to a tobacco product standard in effect under section 907 (21 U.S.C. 387g), and there is a lack of adequate information to justify the deviation from such standard.

The statute provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Scientific review of these applications has demonstrated the following:

- The PMTAs reference a tobacco product master file (TPMF) for information on the ingredients in the VERVE® products. The TPMF includes Chemical Abstract Service (CAS) Registry numbers, percent composition, and target weights expressed in milligrams per unit of product (mg/piece) for each of the ingredients but does not include information on the grade, purity and function of each single ingredient. However, the toxicology review found that none of the single ingredients found in the VERVE® products were present in amounts that raise toxicological concerns, and that no hazards are associated with, or expected from, the ingredients. In addition, the TPMF does not include information on the name, grade, purity, functions, or quantities of the single ingredients for (b) (4) (b) (4), which is found in Verve® Disc products. However, the toxicology review found that the amount of (b) (4) present in the Disc products does not raise toxicological concerns.

- There are adequate process controls and quality assurance procedures to help ensure that the VERVE® products are manufactured consistently to meet the applicant's specifications.

- Based on the ingredients and the HPHCs in the VERVE® products, the toxicological potential is reduced in comparison to cigarettes and smokeless tobacco. Information provided by the applicant showed that the following HPHCs were higher in the VERVE® products than in the comparator products:
    - Arsenic: ↑114% (12.86 ng/portion) in the VERVE® Chews products compared to Marlboro 100's Box cigarettes
    - Free nicotine: ↑1486% (1.04 mg/g) in the VERVE® Discs products compared to chewing tobacco products
    - Total nicotine: ↑36% (0.73 mg/g) in the VERVE® Discs compared to Nicorette gum

However, arsenic levels are not of toxicological concern and the free and total nicotine levels are not expected to impact abuse liability (see, respectively, sections 2.3 and 2.4).

- There were no studies conducted with the VERVE® products to investigate short-term health effects of the products. However, adverse events (AEs) reported in the five clinical studies and reported to the ALCS Consumers Call Center did not identify any serious adverse events (SAEs).

- The pharmacokinetic (PK) profile of the VERVE® products is supportive of a lower abuse liability than consumers' usual brand (UB) cigarettes, as well as supportive of a low risk of initiation or re-initiation of tobacco use by youth, nonusers, and former users.

- In terms of youth risk, the information extrapolating dissolvable tobacco products to VERVE® from the literature and from national survey data support that there is low likelihood of youth initiating tobacco use with the new products. Nonetheless, given the strong evidence regarding the impact of youth marketing exposure to youth appeal and initiation of tobacco use, a marketing authorization should include postmarket requirements to help ensure that youth exposure to tobacco marketing is limited.

- Current smokers who also use one or more other tobacco products are the consumer population most likely to try VERVE® products. Polytobacco use was common in the VERVE® clinical studies submitted in the PMTAs. Given the levels of HPHCs in the products, use of VERVE® products alone would likely lower several biomarkers of exposure (BOE) and biomarkers of potential harm (BOPH) in comparison to smoking cigarettes. Additionally, while smokers who dual use VERVE® products with cigarettes, and do not substantially reduce their cigarettes per day (CPD) (i.e., by 50% or greater), do not reduce their exposure to nicotine or non-nicotine BOE, even a modest reduction in daily cigarette consumption may reduce the risk of tobacco related disease due to decreased exposure to HPHCs.

- Use of VERVE® Chews and Discs products is not associated with significant second-hand exposure which, in this respect, decreases risk for both users and nonusers.

As discussed in more detail in Sections 2.2 through 2.6 of this review, I recommend the PMTAs be authorized.

2. REVIEW OF PMTAS

2.1. Regulatory History

On July 23, 2018, the FDA received four PMTAs from ALCS, submitted on behalf of USSTC. FDA issued Acknowledgement letters to the applicant on August 22, 2018. On September 19, 2018, FDA received the applicant's response (PM0000477) to information requested during a teleconference held on September 5, 2018. FDA issued a Filing letter on February 8, 2019. On February 14, 2019, FDA received an unsolicited amendment containing updates to the PMTAs (PM0000500). FDA issued an Information Request letter on February 20, 2019, detailing the number of samples requested to conduct independent testing of the new tobacco products that are the subject of the PMTAs. FDA issued an Inspection Request letter on February 21, 2019. On February 27, 2019, FDA received the applicant's response to the Information Request letter (PM0000504). On March 7, 2019, FDA received the applicant's response to the Inspection Request letter (PM0000505). On May 8, 2019, FDA received an unsolicited amendment containing corrections to validation reports previously submitted to FDA (PM0000512). This TPL review focuses on whether the data provided by the applicant support marketing

orders for the four VERVE® products

Table 1: Amendments submitted by applicant

STN	Date Received	Amendment Type	Content
PM0000477	September 19, 2018	Minor	Response to FDA's September 5, 2018, teleconference request for information.
PM0000500	February 14, 2019	Minor	Unsolicited amendment to notify FDA of change in manufacturing facility
PM0000504	February 27, 2019	Minor	Response to FDA's February 20, 2019, Information Request letter
PM0000505	March 7, 2019	Minor	Response to FDA/OCE's February 21, 2019, Inspection Request letter
PM0000512	May 8, 2019	Minor	Unsolicited amendment to correct validation reports previously submitted to FDA on September 19, 2018

2.2. Product Composition, Design, and Manufacturing

The subject of the four PMTAs (PM0000470-PM0000473) are oral tobacco products containing United States Pharmacopeia (USP)-grade tobacco-derived nicotine and other ingredients in a chewable form with approximately 1.5 milligrams per piece (mg/piece) of nicotine. The applicant notes that versions of the VERVE® Discs Blue Mint products were marketed in Virginia only. A version identified as Generation (Gen) 1 was a VERVE® Discs Blue Mint first available in May 2012 in a small market in Virginia. Gen 1A had an addition of an (b) (4) . Later in 2013 the texture was modified (Gen 2) and then in 2014 a flavor coating (Gen 3) was added and the new product (VERVE® Discs Blue Mint) was created. The VERVE® Discs Green Mint version was added in 2014, along with other flavors. The VERVE® Chews products were introduced, also in Virginia, in 2015. The applicant states that the current VERVE® Chews products that are the subject of the PMTAs are similar to the original version, with substitution of some flavor ingredients from an alternate supplier and addition of a processing aid to improve machinability.

The ingredient information is cross-referenced to a TPMF ((b) (4)) and includes polymer, non-tobacco cellulose fiber, flavorings, texture modifier, binder, and colorant. These ingredients are commonly used in food products. However, VERVE® Discs products contain a (b) (4) (b) (4)), while the VERVE® Chews products contain (b) (4) , an artificial sweetener. While all new products contain menthol characterizing flavor, the VERVE® Discs Blue Mint product contains higher levels of menthol compared to the levels reported in mentholated cigarettes (↑27%) and smokeless tobacco (↑302%) products (Section 2.3).

As to the design of the new products, both the VERVE® Discs and Chews are thick, teardrop-shaped, and have a soft and flexible texture (VERVE® Chews) or a firm and flexible texture (VERVE® Discs). All four new products are placed in the mouth, chewed, removed, and discarded after use. The new products do not contain a heat source.

The applicant provided, either in the PMTAs or during the facility inspection, details regarding the manufacturing processes for all four VERVE® products. This information supports the determination that the product can be manufactured consistently.

2.2.1. Tobacco Ingredients

The four new VERVE® products are oral tobacco products that do not contain ground, cut, powdered or leaf tobacco. The products do, however, contain tobacco-derived USP-grade nicotine (1.5 mg/piece).

2.2.2. Non-Tobacco Ingredients

As noted in the chemistry review, the applicant provided the ingredient information in a TPMF (b)(4) which was cross-referenced in the PMTAs. These ingredients include polymer, non-tobacco cellulose fiber, flavorings, texture modifier, binder, and colorant. The VERVE® Discs products contain a (b)(4) while the VERVE® Chews products contain (b)(4) an artificial sweetener. While all new products contain menthol characterizing flavor, the VERVE® Discs Blue Mint product (PM0000470) contains higher levels of menthol compared to the levels reported in mentholated cigarettes (↑27%) and smokeless tobacco (↑302%) products. Appendix Tables 13 and 14 include all the non-tobacco ingredients in the four new VERVE® products. Though the referenced TPMF (b)(4) did not demonstrate that food quality of ingredients was used to manufacture the new tobacco products, the applicant notes in the PMTAs that the non-tobacco ingredients are food- or biocompatible medical grade ingredients. As noted in the chemistry review, the regulations that apply to food-grade and biocompatible medical-grade chemicals are not applicable to tobacco products and have not been adopted for tobacco products. The data that informs those designations can, however, be informative to an analysis of the risk of use in oral tobacco products. These will be discussed further in the toxicology section of this review (Section 2.3).

2.2.2.1 Container Closure System Ingredients

The applicant provided container closure system information for the VERVE® Chews and the VERVE® Discs products. According to the applicant, the VERVE® Discs products are packaged in a child-resistant container with a lug finish closure comprising a cap, vial, and label. The vial and cap closure of the Discs products is made of polypropylene resin and colorant. The resin and colorant are pre-mixed and injected into a molding process to achieve the desired color. The label is pre-perforated with a pull tab (tear strip) at the cap and attached to the vial with adhesive. The applicant did not provide the composition of the colorant used in the vial and cap closure resins or composition of the label, adhesive, or ink printed on the label. However, these missing ingredients do not come in direct contact with the new products and therefore do not cause public health concerns.

The VERVE® Chews products are also packaged in a child-resistant container, composed of a button, tube structure, label, and tamper-evident shrink band. The button and tube structure are made from polypropylene resin and colorant that are pre-mixed prior to the injection molding process to achieve the desired color. The label is attached to the tube structure with adhesive. The shrink band is made from polyethylene terephthalate (PET) film and a seaming solution. It is perforated, cut to size for the tube, and individually placed over the closure's opening and button. The tube travels through a heat tunnel to shrink the band in place. The applicant did not provide the composition of the colorant used in the resin molded into button and tube structures or composition of the label, adhesive, or ink printed on the label. However, these missing ingredients do not come in contact with the new products and therefore do not cause public health concerns.

2.2.3. Product Design

The product design, based on chemistry and engineering reviews of the applications, note that the VERVE® Discs and VERVE® Chews are oral products that are thick and teardrop-shaped and have a flexible texture, with the Discs firm and the Chews soft. Both product types are placed in the mouth and chewed; once chewed to satisfaction, the products are removed and discarded. The new products do not contain a heat source. The product components and subcomponents are listed in Table 2 from the engineering review. Figure 1 shows a diagram of the two types (disc and chew) of VERVE® products, as presented in the PMTAs.

Table 2: Product components and subcomponents

Component	Subcomponent	Function and Purpose
Chews (Blue and Green Mint)	N/A	Consumption
Packaging (Chews)	Button	Opens the tube structure
	Tube Structure	Houses the product
	Label	Provides information about the product
	Shrink Band	Tamper evidence for the product
Discs (Blue and Green Mint)	N/A	Consumption
Packaging (Discs)	Cap	Opens the vial
	Vial	Houses the product
	Label	Tamper evidence and information about the product

Figure 1. Product Diagrams (adapted from submission)

According to the engineering review, the target specifications and range limits are used to characterize the products and test data are used to assess whether the products are being made according to the manufacturer's specifications. The applicant provided sufficient information concerning the range limits for design parameters including product height, width, thickness, and piece weight. The VERVE® Chews products have identical range limits for width, height, thickness, and weight, while the VERVE® Discs products have identical physical dimensions but differences in weight. The engineering review presented the applicant's table with design parameters and product dimensions (Table 3).

Table 3: Design parameters for product dimensions (from application)[2]

	Pieces per Container	Height (Length)				Width				Thickness				Container Weight[3] [4]			
		Target Value	Range Limit	Test Data Range[5]	Within Range Limit?	Target Value	Range Limit	Test Data Range	Within Range Limit?	Target Value	Range Limit	Test Data Range	Within Range Limit?	Target Value	Range Limit	Test Data Range	Within Range Limit?
	Count	mm	mm	mm	Yes/No	mm	mm	mm	Yes/No	mm	mm	mm	Yes/No	g	g	g	Yes/No
PM0000470 VERVE® Discs Blue Mint	16	(b) (4)															
PM0000471 VERVE® Chews Blue Mint	12																
PM0000472 VERVE® Discs Green Mint [6]	16																
PM0000473 VERVE® Chews Green Mint	12																

N/A = not applicable as indicated by the applicant

2. [2] The applicant stated that the "product's test results are verified to be in conformance with the requirements for product release as defined" in the table.

3. [3] The 16-piece target weights are (b) grams (Discs Blue Mint) and (b) (4) grams (Discs Green Mint), which corresponds to individual piece weights of approximately 0.532 grams (Discs Blue Mint) and 0.523 grams (Discs Green Mint).

4. [4] The 12-piece target weight is (b) (4) grams, which corresponds to an individual piece weight of approximately 2.1 grams, for all Chews products.

5. [5] The applicant gave a graphical representation of the test data. Based on this graphic, test data values were interpreted. Thus, the symbol (~) was used in the table.

6. [6] Test data were not provided for VERVE® Discs Green Mint. The applicant provided test data that were used to verify that the facility could manufacture the products to meet specifications and states that because the Discs products are manufactured identically, only one Discs product was manufactured and tested. No additional test data are needed for the VERVE® Discs Green Mint.

The blank cells of Table 3 represent information that the applicant did not provide in the applications. While the lack of this information inhibits the ability to fully characterize the products, the information attained during the manufacturing inspection sufficiently addressed the missing information. Table 4 indicates this inspection information. Additional details regarding these data are discussed in the manufacturing section of this review (Section 2.2.4).

Table 4. Dimensional characterization based on inspection documents

	Length	Width	Thickness
VERVE® Discs	(b) (4) mm	(b) (4)) mm	(b) (4)) mm
VERVE® Chews	Not provided	Not provided	(b) (4) mm

2.2.4. Manufacturing, Process, and Controls

The new VERVE® products are manufactured by U.S. Smokeless Tobacco Products LLC at the USSTP D-Pilot Plant, which is located at 4201 Commerce Road, Building D, Richmond, VA 23234. According to the chemistry and engineering reviews, the PMTAs included information regarding the manufacturing processes for both the VERVE® Discs and the VERVE® Chews; however, some information was missing from the PMTAs. The applicant described manufacturing steps and controls but did not provide standard operating procedures (SOPs) or quality documents, in-process parameters, details for the order of addition of ingredients, quality (e.g., grade, purity) of ingredients, and quantity of some ingredients used during manufacturing. The applicant provided specification requirements for nicotine and nicotine-related impurities in the finished products and the results obtained from the performance qualification (PQ) test records were within specifications. During the inspection of the manufacturing facility, this additional information, along with the batch records, was obtained. The batch records (Exhibits #13, #15-16, #19, and #21-22) and documentations (Exhibit #25 through #74) are included in the Establishment Inspection Report (EIR). They contain SOPs, quality documents, in-process parameters, the order of addition of ingredients, and information about other ingredients used during manufacturing. Tables 5 and 6, from the chemistry review, show the parameters required prior to process release of the new VERVE® products.

Table 5: Physical parameters required for product release of the new products

Design Feature	PM0000470 VERVE® Discs Blue Mint			PM0000472 VERVE® Discs Green Mint			PM0000471 and PM0000473 VERVE® Chews Products		
	Low	Target	Upper	Low	Target	Upper	Low	Target	Upper
Piece per Container	(b) (4)								
Weight per Container (g)									
Piece Height (mm)									
Piece Width (mm)									
Piece Thickness (mm)									

N/A = not applicable as indicated by the applicant

Table 6: Chemistry-relevant parameters required for product release of the new products

PMTA	Product Name	(mg/g)	Nicotine Degradant (weight % of nicotine)
PM0000470	VERVE® Discs Blue Mint	(b) (4)	(b) (4)
PM0000471	VERVE® Chews Blue Mint	(b) (4)	
PM0000472	VERVE® Discs Green Mint	(b) (4)	
PM0000473	VERVE® Chews Green Mint	(b) (4)	

Additional manufacturing information was obtained by FDA during the inspection, during which both the chemistry and engineering reviewers were present. According to the engineering review, during the facility inspection, the applicant provided production records for VERVE® Blue Mint Chews and VERVE® Green Mint Discs, as well as explained in detail the manufacturing process for all VERVE® Chews and Discs products.

For the Chews products (b) (4) . As for the VERVE® Chews length and width, (b) (4) , but no specifications on the machine were provided in the application or during the inspection (b) (4)

Inspection documents also showed that the VERVE® Discs products have target specifications for width and length. However, unlike the VERVE® Chews, the VERVE® Discs products do have a target thickness (b) mm with a range of (b)(4) mm). The facility records range limit is tighter than what was provided in the application, demonstrating greater control of the product during manufacturing. Like the VERVE® Discs thickness, the range limits discovered during the inspections are tighter than those submitted in the application, demonstrating a greater control of the product during manufacturing. See EIR Exhibit #19 for more details on the target specifications and range limits for the product dimensions.

Quality control, performance criteria, and test data are interrelated. Quality control establishes the overall monitoring program and identifies testing to be executed; performance criteria describe the methods and pre-specified limits the product must meet; and test data are the result of the testing.

Both the Chews and the Discs products are manufactured at the same facility, the D Pilot Plant in

Richmond, Virginia. The Chews and Discs products are produced under identical manufacturing steps. Process controls were described, and process control parameters were quantified by USSTC. USSTC provided a list of quality control documents detailing the names and numbers of the quality control documents. During the facility inspection, USSTC provided the actual quality control documents that describe the manufacturing steps, process controls, and process control parameters.

The applicant provided test data for both Chews products, but only one of the Discs products (VERVE® Discs Blue Mint). All the provided test data demonstrate that the D Pilot Plant can manufacture the VERVE® products consistently. The applicant states that Discs products are manufactured similarly, and it did not find it was necessary to manufacture and test the VERVE® Discs Green Mint product. Because the applicant stated that both Discs products were produced under identical manufacturing steps and with similar degrees of consistency, test data for both Chews products and Discs Blue Mint was considered sufficient by the engineering reviewer.

After the manufacturing inspection, the engineering review concluded that no additional information was needed regarding the dimensional characterization of the VERVE® Chews and Discs products.

2.2.5. FDA Sample Testing

The testing methods for the VERVE® products were provided to FDA in amendment PM0000477, following a teleconference with the company after identifying missing information in the PMTAs. This information was needed for the analysis of the products by the FDA's Southeast Tobacco Laboratory (STL). In accordance with section 910(b)(1)(E) of the FD&C Act, samples of the four new VERVE® products were received by STL on March 5, 2019, in support of these PMTAs. Table 7 shows the quantities of the samples that were submitted to STL. Table 8 shows the test requests made by FDA for each of the four VERVE® products and control samples.

Table 7: Samples submitted by USSTC to STL

Tobacco Product Samples				
PMTA STN	**Tobacco Product Name**	**Total Quantity Per Lot**	**Number of Lots**	**Total Quantity Needed**
PM0000470	VERVE® Discs Blue Mint	20 vials	3	60 vials
PM0000471	VERVE® Chews Blue Mint	20 containers		60 containers
PM0000472	VERVE® Discs Green Mint	28 vials		84 vials
PM0000473	VERVE® Chews Green Mint	18 containers		54 containers

Control Samples			
Control Sample Name	**Total Quantity Per Lot**	**Number of Lots**	**Total Quantity Needed**
VERVE® Discs monitor sample	N/A		15 pieces
VERVE® Discs Placebo			39 pieces
VERVE® Chews Placebo			25 pieces
Monitor sample			129 grams

Table 8: Testing requested of STL by FDA

Test Requested	VERVE® Discs Blue Mint	VERVE® Chews Blue Mint	VERVE® Discs Green Mint	VERVE® Chews Green Mint
Chemistry Test Requests				
Nicotine (total & free)	✓	✓	✓	✓
pH	✓	✓	✓	✓
Cadmium	✓			
NNN			✓	
NNK			✓	
Formaldehyde		✓	✓	
Acetaldehyde		✓	✓	
Arsenic				✓
Microbiology Test Requests				
Water activity (a_w)	✓	✓	✓	✓
Physical Test Requests				
Portion mass	✓	✓	✓	✓
Portion height, width, and thickness	✓	✓	✓	✓
Pieces per container	✓	✓	✓	✓

The results of the STL testing show that the testing data are lower compared to the data included in the PMTAs except for arsenic in the VERVE® Chews products and pH and free nicotine in the VERVE® Discs products. The level of arsenic determined by STL in the VERVE® Chews products is 14% or 1.58 ng/g higher compared to the PMTAs. The pH measured in the VERVE® Discs products by STL is 9% or 0.67 higher compared to the PMTAs. Subsequently, for free nicotine, the level calculated by STL in the VERVE® Discs products is 110% or 0.9 mg/g higher compared to the level noted in the PMTAs. However, compared to the measured data in Nicorette Gum, published data for General Snus smokeless tobacco, and FDA internal data (n=3 to 242) for other smokeless tobacco products, the levels of arsenic in the VERVE® Chews products and pH and free nicotine in the VERVE® Discs products are comparable or lower. These data are presented in Table 9.

Table 9: Comparison of HPHC levels in the PMTAs to the STL testing results

Constituent	VERVE® Discs (PM0000470, PM0000472)			VERVE® Chews (PM0000471, PM0000473)		
	PMTA Mean (SD)	STL Mean (SD)	% Change[a]	PMTA Mean (SD)	STL Mean (SD)	% Change[a]
Nicotine (total), mg/g	2.62 (0.09)	2.51 (0.01)	↓4	0.67 (0.01)	0.57 (0.03)[*]	↓15
Nicotine (free), mg/g	0.82 (0.06)	1.72 (0.03)	↑110	0.02 (0.00)	0.01 (0.00)	↓50
pH	7.67 (0.03)	8.34 (0.00)	↑9	6.35 (0.10)	6.21 (0.02)	↓2
Cadmium, ng/g	14.67 (3.31)	BLOQ[§]		N/D		
Arsenic, ng/g	N/D			11.04 (0.30)	12.62 (0.53)[+]	↑14
NNN, ng/g	2.05 (0.80)	N/D	↓100	BLOQ		
NNK, ng/g	0.70 (0.03)	0.63 (0.17)[§§]	↓10	BLOQ		
Formaldehyde, µg/g	1.00 (0.00)	0.12 (0.008) [§§]	↓88	0.22 (0.04)	0.054 (0.002)[++]	↓75
Acetaldehyde, µg/g	0.53 (0.08)	0.063 (0.003) [§§]	↓88	0.20 (0.00)0.27	0.078 (0.006)[++]	↓61

BLOQ = below limit of quantitation; N/D = not detected

[a] % Change = ([STL mean constituent (all batches, unit/g of product)] – [PMTA mean constituent (unit/g of product)])/[PMTA mean (unit/g of product)]

[*] Not within the nicotine specification limits of (b) (4)) mg/g for VERVE® Chews products (PM0000471, PM0000473)

[+] Arsenic was only tested in VERVE® Chews Green Mint

[++]Formaldehyde and acetaldehyde were only tested in VERVE® Chews Blue Mint

[§]Cadmium was only tested in VERVE® Discs Blue Mint

[§§]NNN, NNK, formaldehyde, and acetaldehyde were only tested in VERVE® Discs Green Mint

An independent analysis of the finished new tobacco products' water activity (a_w) was conducted by the FDA's Office of Regulatory Affairs (ORA) Southeast Food and Feed Laboratory (SFFL); results are presented in Table 10. The average results (VERVE® Discs Blue Mint: 0.266, VERVE® Chews Blue Mint: 0.540, VERVE® Discs Green Mint: 0.266, VERVE® Chews Green Mint: 0.541), while analytically variable (14 to 21%) from the applicant-provided data, are similar to the values provided by the applicant for each new tobacco product at the initial storage time point (VERVE® Discs Blue Mint:(b) (4) , VERVE® Chews Blue Mint:(b) (4) , VERVE® Discs Green Mint:(b) (4) , VERVE® Chews Green Mint: (b) (4)). In addition, the a_w values for all new tobacco products, tested by SFFL, are below what has been reported to support microbial proliferation ((b) (4)).

Table 10: Product stability: Water activity initial sampling compared to STL results

PMTA	Water Activity (a_w)	
	PMTA Data[a]	SFFL Testing
PM0000470 (VERVE® Discs Blue Mint)	(b) (4)	0.266
PM0000471 (VERVE® Chews Blue Mint)		0.540
PM0000472 (VERVE® Discs Green Mint)		0.266
PM0000473 (VERVE® Chews Green Mint)		0.541

[a] Initial sampling from PMTA data

STL also measured the portion length, portion width, portion thickness, portion mass, and the number of pieces per container for the new products. Table11 conveys the results from STL physical parameter testing.

Table 11: FDA sample product testing

PM#	Parameter	Replicates	STL Results			Applicant's Range Limits (from application)
			Tube 1	Tube 2	Tube 3	
PM0000470 VERVE® Discs Blue Mint	Length (mm)	1	13.91	14.50	14.86	(b)(4)
		2	14.38	14.56	14.43	
		3	14.58	14.67	14.68	
	Width (mm)	1	12.46	12.18	12.49	
		2	12.85	12.14	12.33	
		3	12.90	12.18	12.28	
	Thickness (mm)	1	3.22	3.00	3.24	
		2	3.18	3.15	3.19	
		3	3.24	3.24	3.18	
	Portion Mass (g)	1	0.50469	0.51514	0.54127	
		2	0.53892	0.54337	0.51247	
		3	0.55834	0.53677	0.51546	
	Container Weight (g)		8.42698	8.35991	8.30632	
	Pieces per Container (#)		16	16	16	16
PM0000471 VERVE® Chews Blue Mint	Length (mm)	1	20.60	20.13	N/A	(b)(4)
		2	20.77	20.12	N/A	
		3	20.68	20.47	N/A	
	Width (mm)	1	17.33	16.35	N/A	
		2	17.12	16.41	N/A	
		3	16.99	16.55	N/A	
	Thickness (mm)	1	8.12	9.19	N/A	
		2	7.82	9.36	N/A	
		3	8.37	9.00	N/A	
	Portion Mass (g)	1	2.13048	2.11467	N/A	
		2	2.13036	2.12807	N/A	
		3	2.09368	2.15748	N/A	
	Container Weight (g)		25.03287	25.26524	N/A	
	Pieces per Container (#)		12	12	N/A	12
PM0000472 VERVE® Discs Green Mint	Length (mm)	1	14.49	14.34	15.05	(b)(4)
		2	15.02	14.60	15.06	
		3	15.02	14.66	14.79	
	Width (mm)	1	11.96	12.12	12.52	
		2	12.04	11.95	12.63	
		3	11.97	12.38	12.36	
	Thickness (mm)	1	3.18	3.25	3.13	
		2	3.30	3.24	3.23	
		3	3.28	3.17	3.18	
	Portion Mass (g)	1	0.49669	0.51468	0.51259	
		2	0.53205	0.51327	0.53645	
		3	0.53460	0.52036	0.51142	
	Container Weight (g)		8.39159	8.31329	8.23770	
	Pieces per Container (#)		16	16	16	16

PM#	Parameter	Replicates	STL Results			Applicant's Range Limits (from application)
			Tube 1	Tube 2	Tube 3	
PM0000473 VERVE® Chews Green Mint	Length (mm)	1	19.77	19.99	20.32	(b) (4)
		2	19.98	20.43	20.22	
		3	20.10	18.99	20.08	
	Width (mm)	1	16.95	16.27	16.68	
		2	16.66	16.32	16.28	
		3	16.65	16.28	16.34	
	Thickness (mm)	1	9.43	9.33	9.24	
		2	9.41	9.15	9.16	
		3	8.55	8.87	9.18	
	Portion Mass (g)	1	2.17920	2.03758	2.15118	
		2	2.14744	2.13103	2.06575	
		3	2.06498	1.98820	2.08724	
	Container Weight (g)		25.36221	25.23216	25.29342	
	Pieces per Container (#)		12	12	12	12

All the STL data points fall within the applicant's established parameter range limits, which typically illustrate parameters that meet the product attributes. Range limits are used to characterize the product based on the target specifications and product attributes. Therefore, product test data should meet these range limits; if not, the product should be discarded or reprocessed to resolve the deviation. The test data show that the applicant can consistently manufacture the VERVE® products per their specifications. No further information is needed regarding the sample test data.

The chemistry, microbiology, and engineering reviews each concluded that the independent FDA testing of the products was consistent with the data submitted by the applicant.

2.2.6. Product Stability

The microbiology review noted that the applicant provided data from stability studies carried out under two conditions: a long-term condition ((b) (4)) measured over a (b) (4) period and an accelerated condition ((b) (4)) measured over a (b) (4) period. The studies assess the changes in nicotine, nicotine impurities (myosmine, nornicotine, cotinine, anatabine, nicotine-N'-oxide, β-nicotyrine, and anabasine), water activity, and pH. Overall, the levels of nicotine and nicotine-related impurities increased with the increase of storage times and temperatures. However, these increases are within the specification limits of nicotine and nicotine-related impurities. Both the microbiology and chemistry reviews determined that the submitted stability data support a proposed (b) (4) shelf life.

According to the microbiology review, the applicant indicated that the shelf-life of the new tobacco products was determined by the levels of nicotine degradants and impurities over a (b) (4) period. The levels of these degradants were within established limits during this storage time. In addition, a microbiological examination for microbial content was conducted during this period and no increases in microbial content were observed. Therefore, the shelf-life for the new tobacco products was set at (b)(4) (b) (4)). To assess microbiological stability during this shelf-life period, the applicant provided adequate stability data. The parameters analyzed in this review to determine microbial stability were water activity (a_w), tobacco-specific nitrosamine (TSNA) content, and microbial count data. In addition, comparisons of the applicant-provided stability data with known available tobacco product (smokeless tobacco products, cigarettes) data (published literature or applicant-provided) were conducted.

The data provided by the applicant were collected from either long-term [(b) (4) e (b) (4) (a_w and TSNAs)] or accelerated [(b) (4) (a_w only)] conditions. The applicant provided a_w data for the new tobacco products over a (b) (4) storage period. These data are presented in Table 12. Analysis of the long-term data for the new tobacco products indicated increases in a_w of the new tobacco products during storage (VERVE® Discs Blue Mint: 17%, VERVE Chews Blue Mint: 11%, VERVE® Discs Green Mint: 42%, VERVE® Chews Green Mint: 13%). Analysis of the accelerated data for the new tobacco products indicated increases in a_w of the new tobacco products during storage (VERVE® Discs Blue Mint: 61%, VERVE® Chews Blue Mint: 17%, VERVE® Discs Green Mint: 52%, VERVE® Chews Green Mint: 15%). While increases in a_w over storage raise concerns about microbial stability, the value of the highest reported a_w data (b) (4) associated with any of the new tobacco products is less than the minimum a_w (b) (4) necessary to support microbial activity.

Table 12. Product stability: Water activity over storage time

PMTA	Long-Term		Accelerated	
	Time (Months)	Water Activity (a_w)	Time (Months)	Water Activity (a_w)
PM0000470 (VERVE® Discs Blue Mint)	(b) (4)			
	% Change over time	↑17	**% Change over time**	↑61
PM0000471 (VERVE® Chews Blue Mint)	(b) (4)			
	% Change over time	↑11	**% Change over time**	↑17
PM0000472 (VERVE® Discs Green Mint)	(b) (4)			
	% Change over time	↑42	**% Change over time**	↑52
PM0000473 (VERVE® Chews Green Mint)	(b) (4)			
	% Change over time	↑13	**% Change over time**	↑15

The applicant provided microbial count data for the new tobacco products over a (b) (4) storage period. The applicant evaluated aerobic plate counts (APC), coliforms, *Escherichia coli*, yeast and mold counts, and the presence of *Salmonella* spp. or *Listeria* spp. The level of microbial content at each point tested was either below the limit of detection or was slightly above detectable levels (b) (4) colony forming units (cfu)/g). These microbial levels of the new tobacco products are not of concern from a microbiology perspective.

The applicant provided TSNA data including N-nitrosanabasine (NAB), N-nitrosoanatabine (NAT), N-nitrosonornicotine (NNN), and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) over a (b) (4) storage period. The new tobacco products showed increases in NNN for VERVE® Discs Blue Mint (14%) and VERVE® Discs Green Mint (4%) and NNK for VERVE® Discs Blue Mint (41%) and VERVE® Discs Green Mint.[7] For VERVE® Chews Blue Mint and VERVE® Chews Green Mint, no changes in NNN and NNK were

7. [7] A percentage increase could not be determined because the one-month time point was Below Limit of Quantitation (BLOQ).

indicated because the target constituents were not detected or were below the limit of quantitation (BLOQ). For all new tobacco products, no changes in NAB and NAT were indicated because the target constituents were not detected or were BLOQ. However, any increase in TSNA content over the storage duration of a product containing tobacco-derived material is a potential concern. Because the water activity (a_w) of the new tobacco products does not support microbial activity, and there is a demonstrated absence of microbial content of the new tobacco products, changes in TSNA levels are not likely due to microbial-mediated TSNA formation during storage. For these reasons, including the manufacturing quality controls (see section 3.4), the overall microbial stability, product quality, and manufacture of the new tobacco products, TSNAs are not of concern from a microbiology perspective.

The applicant-provided microbial count data of the new tobacco products were compared to microbial data of smokeless tobacco products (loose or portioned moist snuff, dry snuff, snus or chewing tobacco). Comparison of the new tobacco products' microbial content with smokeless tobacco products' microbial content yielded differences in the microbial load of the products, with lower microbial load in the new tobacco products. While high microbial content in the smokeless tobacco products could lead to the formation of microbial-mediated TSNAs, the likelihood of this process in the new tobacco products is not expected because the microbial content is at or below detectable limits.

The applicant also provided comparator TSNA data for an oral nicotine product, Nicorette®, a smokeless tobacco product, General® snus, and cigarettes. However, because of the low a_w ((b) (4)) and microbial content of the new tobacco products (the microbial content is near the lower limit of detection), the increases in NNN and NNK content as compared to Nicorette® are not of concern from a microbiology perspective. When the maximum NNN and NNK content at any test point of the new tobacco products was compared to those of either General® snus or cigarettes, decreases in NNN and NNK content were observed in the new tobacco products.

The chemistry and microbiology reviews conclude that the available microbiological data provide support that the new tobacco products are stable for at least (b) (4) .

2.2.7. Inspections of Manufacturing Facilities

FDA conducted an inspection of the applicant's manufacturing facility on June 18-20, 2019 to confirm the manufacturing information submitted in the PMTAs and determine whether the products can be consistently produced. No inspectional observations (Form FDA 483) were issued at the conclusion of the visit. The EIR documents a "No Action Indicated" classification for this visit.

2.2.8. Summary of Composition, Design, and Manufacturing Findings

The engineering review concluded that, given the totality of the evidence provided regarding the design specifications, test data, manufacturing process, quality control, and quality control parameters, the PMTAs contain adequate information regarding the following:

- A description of the principles of operation of the products
- An adequate description of the products
- Sufficient quality control test data
- Sufficient information in the description of product manufacturing processes, including process controls and quality assurance procedures, in addition to the information provided in amendments and inspection documents, to ensure that the product is manufactured in a consistent manner

As TPL, I agree with the engineering conclusions that these PMTAs contain sufficient information to characterize the product design and adequate processes and controls to help ensure that the products meet the manufacturer's specifications.

The chemistry review concluded that these PMTAs contain adequate information with respect to the following:

- Data on chemical stability of the new products stored under long-term (b) (4)) and accelerated ((b) (4)) conditions
- Data on HPHC measurements of the new products over a (b) (4) period compared to cigarettes
- Data on HPHC measurements of Nicorette Fresh Mint Gum

The chemistry review does discuss the increase of the level of arsenic reported by STL in the VERVE® Chews products. This is addressed in Section 2.3.

The chemistry PMTA and TPMF reviews note two issues that the reviewer identified as requiring clarification:

- The applicant did not provide bioanalytical testing information used in the biomarkers of exposure (BOE) study or scientific evidence and rationale for how the BOE of the Generation 2 (Gen 2) product of the VERVE® Discs Blue Mint is appropriate to extrapolate to the new products. The review concludes that the following deficiency should be conveyed to the applicant:
    1. Your PMTAs include BOE data in humans, but not bioanalytical methods used in the study. In addition, you did not provide an explanation or scientific evidence and rationale for using the Gen 2 product in place of the VERVE® Discs Blue Mint and for how the use of the Gen 2 product can be extrapolated to represent BOE to the VERVE® Discs Blue Mint and other three VERVE® products (VERVE® Discs Green Mint, VERVE® Chews Blue Mint, and VERVE® Chews Green Mint). In order to evaluate the suitability and acceptability of the BOE study and the impact of this study on public health, provide the following information:
        a. An explanation or scientific evidence and rationale for using the Gen 2 product in place of the VERVE® Discs Blue Mint and on how the BOE of the Gen 2 product can be extrapolated to the VERVE® Discs Blue Mint, VERVE® Discs Green Mint, VERVE® Chews Blue Mint, and VERVE® Chews Green Mint products.
        b. Testing information used to analyze urine BOE, creatinine, and blood carboxyhemoglobin (COHb) including but not limited to bioanalytical test protocols and methods, validation reports, testing laboratory information, and relevant laboratory accreditation or certification.

- The TPMF did not provide the grade, purity, and function for each ingredient. In addition, the applicant did not provide the name, grade, purity, functions, or quantities of the single ingredients in (b) (4). The chemistry TPMF review concludes that the following deficiency should be conveyed to the TPMF owner:

    1. Your TPMF provided the CAS numbers, percent composition, and target weights expressed in milligrams per unit of product (mg/piece) for each of the non-tobacco ingredients in support of the referenced submissions. However, your TPMF did not provide the grade, purity, and function for each ingredient. In addition, you did not provide the name, grade, purity, functions, or quantities of the single ingredients in (b) (4)

> Because the PMTA products are uniquely composed of single and complex ingredients and manufacturing processes and controls that are not commonly used in tobacco products, the grade, purity, and function of these ingredients are necessary to ensure appropriate quality (e.g., food grade, generally recognized as safe [GRAS[8]]); and for FDA to understand how each ingredient is used in the manufacturing of the PMTA products. Provide the grade, purity, function, for each of the listed ingredients and the complete listing of single ingredients for (b) (4) . Without this information, we cannot assess the overall impact of the PMTA products on the public health.

The chemistry review states that the TPMF lacks information on the grade, purity, and function of each ingredient and single ingredients in (b) (4) However, scientific review of the single ingredients and individual components of (b) (4) indicate that none of the ingredients in the new tobacco products are present in amounts that raise toxicological concerns (Section 2.3). Further, sufficient information regarding the manufacturing processes and controls that can affect the product composition, chemical stability, and HPHC levels was provided to demonstrate the products meet the manufacturer's specifications. Therefore, the deficiency of information on grade, purity, and function of ingredients need not be conveyed to the applicant.

Regarding the bioanalytical testing methods for the BOE measurements, the Behavioral and Clinical Pharmacology (BCP) reviewer was not concerned with the lack of information regarding the methods. There was limited BOE information, primarily showing nicotine content in similar prototype and precursor products that was able to be bridged to the candidate PMTA products. In addition, the reviewer felt there was sufficient information from the literature for other oral nicotine products and reference data regarding HPHCs from the chemistry review to provide confidence in the BOE and use behavior for VERVE® and similar products (section 2.4). While it is beneficial for an applicant to supply the bioanalytical testing methods for biomarkers studied with PMTA products for FDA to review, as TPL, I agree that it is not necessary that a deficiency for this issue be conveyed.

The microbiology review concluded that the applicant provided adequate microbiology-related information to demonstrate product stability. As TPL, I agree with the microbiology conclusions.

The OCE manufacturing review identified no significant compliance issues during the manufacturing inspection conducted, and no observations were issued at the time of inspection.

2.3. Toxicological Risk Assessment

No original toxicology studies were submitted by the applicant for any of the VERVE® products. The applicant provided toxicological assessments, which included hazard and exposure assessments of the ingredients associated with VERVE® Discs and Chews. The exposure assessments relied on toxicity values intended for foods as derived by regulatory and industrial trade associations; as such, these values are not intended for tobacco products. Nonetheless, based on the data from oral exposure studies and the estimated exposures to ingredients made by the applicant from the use of VERVE®, the information supported the determination that the added ingredients were not of toxicological concern given the margins of exposure in relation to oral toxicity studies derived from published reference values. A literature review based on published best practices for systematic reviews (Institute of Medicine [IOM], Cochrane, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]) was also provided by the applicant, including chemical and nonclinical endpoints related to potential health

8. [8] GRAS designation does not apply to tobacco products.

effects. No novel health or toxicological concerns for VERVE® were identified as a result of this systematic literature review conducted by the applicant.

2.3.1. Harmful and Potentially Harmful Constituents

The applicant also measured nine analytes included on the abbreviated HPHC list for smokeless tobacco products A toxicological assessment of the VERVE® products can be greatly informed by the measurement of HPHCs in the products and comparison of those values with other tobacco products, primarily cigarettes and snus. The chemistry review provided evaluation of the applicant's HPHC measurements; comparisons across tobacco products are presented in Appendix Tables 16 and 17.

Evaluation of HPHCs in the New Products

The applicant claimed that because the new products do not meet the definition of a "smokeless tobacco product" and in the absence of specific guidance, the applicant only evaluated constituents in the new products that are listed in the abbreviated list of HPHCs for smokeless tobacco from the 2012 Draft Guidance.[9] This is a reasonable approach as HPHCs listed for combustible cigarettes are not expected in the VERVE® products. The applicant provided complete datasets for nine HPHCs from the FDA abbreviated HPHC list for smokeless tobacco products that includes nicotine (total and free), cadmium, arsenic, benzo[a]pyrene (B[a]P), formaldehyde, acetaldehyde, crotonaldehyde, NNN, and NNK. The applicant also provided measurements for pH, portion weight, NAT, and NAB. The applicant stated that the portion weight was used to convert the measured per-gram quantity to the reported per-portion quantity in cases where a single piece is not used for analysis.

HPHC Experimental Design

The applicant also provided HPHC measurements using the same three production lots of the new products employed in the stability studies. Each production lot was stored in the respective packaging at (b) (4) (namely long-term conditions) and tested in seven replicates (n=7) at three different time points. The first time point was conducted once the samples were received by the testing laboratory, between 7 and 30 days (termed 1 month or T=1M), post-manufacturing. Samples were stored in an environmental chamber at (b) (4) (b) (4) and tested at (b) (4) and (b) (4) post-manufacturing. This information is presented in Appendix Table 18.

HPHC Test Methods

The applicant stated that (b) (4)), an ISO 17025:2005 accredited laboratory, conducted chemical and physical testing at Altria's Center for Research and Technology (CRT) in Richmond, VA, using the following analytical methods:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

9. [9] Draft Guidance for Industry (2012). https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm297828.pdf

- (b) (4)
- (b) (4)
- (b) (4) t

The PMTAs included quantitative protocols, validation summaries, validation reports, and relevant work instructions necessary to evaluate the analytical methods used. The applicant implemented a retrospective data verification of the raw data and identified incorrect entries in the validation reports for TSNAs, cadmium and arsenic (supplemental). On May 8, 2019, the applicant submitted an unsolicited amendment, PM0000512, correcting the information in the validation reports. From a chemistry perspective, the information provided about the analytical testing methods is acceptable.

Evaluation of HPHC Test Data for the New Products

The PMTAs included the summaries of measured HPHCs, individual HPHC measurements, and the limits of quantitation (LOQs) for each analytical method and product type.

The mean average and standard deviation across the three production lots of the new products for each of the measured HPHCs at each time point are presented in Appendix Table 18. In the chemistry review, the mean average and standard deviation across the three production lots of the new products are calculated based on measured HPHC values that are at least equal to or above the method LOQ. For measured values below the method LOQ, the data are omitted in determining the mean average and standard deviation. If only one data point is detected at or above LOQ, no standard deviation is reported. The quantity of each HPHC is expressed in milligrams per portion (piece) of product (mg/portion) and % RSD (across lots and replicates) above 20% are in bold text in Appendix Table 18. The relative change (%) in HPHC levels at time points T=6M and T=12M compared to T=1M is also included.

Each HPHC is discussed below. This discussion includes the measured levels in the VERVE® products, both those presented by the applicant (at 1M, 6M and 12M) and those measured by STL. The HPHC levels in comparison to cigarette smoke, smokeless tobacco, and NRT are also presented in each section, when applicable. The applicant provided data for three comparator products (Nicorette Fresh Mint Gum, General Snus, and Marlboro 100's Box cigarettes) expressed in amount per portion (Appendix Tables 15 and 16). The chemistry review also used internal FDA data for other smokeless tobacco products as a comparator for the new products (Appendix Table 17). The product stability of nicotine and nicotine degradation and impurity is also discussed here, as well as previously in section 2.2.6 of this review. The toxicological potential of these HPHCs in the VERVE® products, especially in comparison to cigarettes, is discussed below.

Acetaldehyde - A decrease in acetaldehyde over time was seen in the VERVE® Discs products at both 6M and 12M compared to 1M (0.06-0.51 mg/portion below 1M levels). However, an increase in acetaldehyde was seen in the VERVE® Chews products at both 6M and 12 M, 30-90% (0.1-0.27 mg/portion). The amount of acetaldehyde measured in VERVE® Discs and Chews products is 94% less than acetaldehyde measured in General Snus and > 99% less than acetaldehyde measured in cigarettes (Appendix Table 16).

Arsenic - Over the 12-month testing period, arsenic was not detected in the VERVE® Discs products. Arsenic is one of only two HPHCs for which the applicant's comparator data show higher levels in the VERVE® Chews; the arsenic level is higher in the VERVE® Chews by 114% (12.86 ng/portion) compared to Marlboro 100's Box cigarettes on a per-portion basis. However, when normalized to ng/g of product

(wet weight basis [WWB]), the level of arsenic detected is close to the level of arsenic measured in the comparator cigarettes (↑2% or 0.21 ng/g). The mean arsenic level in the VERVE® Chews measurement from STL was 14% higher than the mean level in the PMTAs. This equates to a 12% or 1.32 ng/g higher arsenic level in the VERVE® Chews products reported by STL compared to Marlboro 100's Box cigarettes. However, the arsenic level reported by STL in the VERVE® Chews products is lower than the measured levels in Nicorette Gum, General Snus (Appendix Table 16) and FDA internal data for chewing tobacco, dissolvables, moist snuff, and snus tobacco products with similar daily usage patterns.

The toxicology review addressed the potential for toxicological concern from the increased arsenic in the VERVE® Chews products as compared to Marlboro 100's Box cigarettes. Arsenic is a constituent with both non-cancer toxicity and carcinogenic potential, including for oral cancer (1, 2).

Non-cancer toxicity
Arsenic exposure is evaluated in terms of reference dose (RfD) and daily exposure to arsenic through diet and water consumption. U.S. EPA set the arsenic standard for drinking water at 10 ppb (0.01 mg/L (3)). FDA CFSAN set an action level of 10 ppb, or 10 ug/kg, for arsenic in apple juice (1). This level was set based on chronic exposure to the toxicant (0-50 years) and urinary tract and lung cancer disease rates. The previous action level of 23 ppb was determined based on short-term exposure and non-cancer endpoints.

The oral toxicity RfD for arsenic estimated by US EPA is $3.0x10^{-4}$ mg/kg/day. This RfD is based upon possible cardiovascular and dermal toxicities (2). Conservatively assuming consumption of one tube of VERVE® Chews per day (12 pieces; 1 piece = 1 portion) with the upper bound of reported arsenic as 24.16 ng/portion, or 290 ng arsenic per tube, the estimated daily exposure level is $4.0x10^{-7}$ mg/kg/day for a 60 kg individual (750 times lower than the RfD), per the following formula:

Daily exposure on a per kg body weight basis [mg/(kg/day)] =
[Daily exposure to ingredient/60 kg]

Mean daily intake of arsenic through diet in adults has been estimated to range between 0.0167 and 0.129 mg/day (WHO, 2015). For an individual who weighs 60 kg, this indicates an exposure rate of $2.8x10^{-4}$ to $2.2x10^{-3}$ mg/kg/day. In contrast, the arsenic exposure level in VERVE® Chews based on the upper bound of arsenic measurement is $4.0x10^{-7}$ mg/kg/day. Therefore, despite the increase compared to Marlboro 100's Box cigarettes, arsenic levels in VERVE® Chews compared to cigarettes do not raise non-cancer toxicological concerns.

Carcinogenicity
Higher levels of arsenic were measured in the VERVE® Chews products when compared to combusted cigarettes. However, exposure to cigarette smoke and oral nicotine or smokeless tobacco products is through different routes (oral vs. inhalation). There may be differences in HPHC bioavailability and target tissues for carcinogenic effects associated with user exposures to carcinogens from cigarettes versus the VERVE® Chews products, and therefore it is likely that users would exhibit different biological responses to exposure to a given constituent from the VERVE® products or cigarettes. This aspect does introduce some uncertainty of the risk from exposure to arsenic in inhaled versus oral tobacco products. Furthermore, the applicant notes that an average use of VERVE® Chews is 6 per day versus 12, which comprises a whole tube. Thus, the overall daily usage of the product may be less than an entire tube over the time a user consumes the product. Daily variation in product use can also contribute uncertainty regarding the exposure to arsenic, as can the form of the oral tobacco product or NRT (e.g., chew, disc, gum), which can impact arsenic levels and hazards presented by each product.

U.S. EPA IRIS gives an oral slope factor of 1.5 mg/kg/day for arsenic (2). The estimated daily exposure level of arsenic from the highest level of arsenic measured in an entire tube of VERVE® Chews is $4.0x10^{-7}$ mg/kg/day for a 60 kg individual. Multiplying the oral slope factor by the estimated daily exposure level of arsenic in VERVE® Chews results in a lifetime cancer risk of $6.0x10^{-7}$. Conversely, if a tobacco user consumed the same number of Nicorette® Fresh Gum (756.8 ng arsenic, so $1.26x10^{-5}$ mg/kg/day for a 60 kg individual), the lifetime cancer risk is $1.9x10^{-5}$. Thus, according to this calculation, the lifetime cancer risk from Nicorette® Fresh Gum is 32 times higher than that of VERVE® Chews.

The HPHC data submitted by the applicant also demonstrates potential for reduced toxicant exposure from the VERVE® products compared to the comparator products (Nicorette® Gum, General Snus, and Marlboro 100's Box cigarettes), given the low levels or absence of some constituents (Appendix Table 15). Additionally, when the applicant compared arsenic levels in VERVE® Chews to those in General Snus and Nicorette® Gum (which are through oral exposure), the levels of arsenic in VERVE® Chews were lower on a per-product basis by 51% and 68%, respectively. When compared to internal FDA data (Appendix Table 17), the levels of arsenic were lower (as calculated by the chemistry reviewer) in VERVE® Chews than in smokeless tobacco products as follows (Appendix Table 17):

- Chewing Tobacco: VERVE® Chews ↓97% in arsenic
- Dissolvables: VERVE® Chews ↓94% in arsenic
- Moist Snuff: VERVE® Chews ↓ 95% arsenic
- Snus: VERVE® Chews ↓91% arsenic

In spite of the differences in exposure routes between the new products and cigarettes and considering the available epidemiological data on risks of lung cancer and respiratory disease from smokeless tobacco products compared to combusted cigarettes (4), it is reasonably likely that users are not subject to excess risk from the levels of arsenic present in the new VERVE® products. Therefore, despite the higher arsenic levels compared to Marlboro 100's Box cigarettes, arsenic levels in VERVE® Chews do not raise toxicological concerns.

Benzo[a]pyrene – Over the 12-month testing period, B[a]p was not detected in any of the VERVE® products. Benzo[a]pyrene is measured to be 21 ng/g in cigarettes (Appendix Table 16)

Cadmium – Over the 12-month testing period, cadmium was not detected in the VERVE® Chews products. In the VERVE® Discs Blue Mint there was an increase of 42% (3.6 ng/portion) at 12M. In the VERVE® Discs Blue Mint at 6M and the VERVE® Discs Green Mint at both 6M and 12M, there was a decrease in cadmium over time of 26-29% (2.11-2.17 ng/portion). From a chemistry perspective, the 42% increase in cadmium (12M, VERVE® Discs Blue Mint) may be due to the variability in the analytical measurements, where the %RSD is 57% (see bolded text in Appendix Table 18). The amount of cadmium measured in VERVE® Discs and Chews products is 87% less than cadmium measured in General Snus and 80% less than cadmium measured in cigarettes (Appendix Table 16).

Crotonaldehyde – Over the 12-month testing period, crotonaldehyde was not detected in any of the VERVE® products. Crotonaldehyde is measured in General Snus and Marlboro 100' Box at concentrations of 0.69 µg/g and 59 µg/g, respectively (Appendix Table 16).

Formaldehyde – A decrease in formaldehyde was seen in the VERVE® Discs products at both 6M and 12M ranging from 35-81% (0.3-0.7 mg/portion) below 1M levels. A reduction of 16% (0.07 mg/portion) at 6M was seen in the VERVE® Chews Blue Mint, and a reduction of 17-18% (0.1-0.11 mg/portion) was seen in VERVE® Chews Green Mint at 6M and 12M. These changes over time do not cause concern for public health because formaldehyde is decreased. Moreover, the amount of formaldehyde measured in

VERVE® Discs and Chews products is 70% less than formaldehyde measured in General Snus and 98% less than formaldehyde measured in cigarettes (Appendix Table 16).

Nicotine – When comparing 12M or 6M to 1M, free nicotine decreased over time in the VERVE® Discs by 24-44% (0.14-0.25 mg/portion). Free nicotine in the VERVE® Chews also decreased over time, by 40-80% (0.02-0.06 mg/portion). Nicotine is the other HPHC for which levels are higher according to the applicant's comparator information; total nicotine higher by 36% (0.73 ng/g) in the VERVE® Discs products compared to Nicorette gum. However, free nicotine is lower by 45% in the VERVE® products compared to Nicorette gum, along with 22% lower pH in the VERVE® products compared to Nicorette gum. When compared to smokeless tobacco, the free nicotine is higher by 1486% (1.04 mg/g) in the VERVE® Discs compared to chewing tobacco, along with 29% (1.76) higher in pH in the VERVE® Discs in comparison with chewing tobacco.

For the VERVE® Discs products, the pH and free nicotine are higher by 9% (0.67) and 110% (0.9 mg/g), respectively, as measured by STL compared to the levels determined by the applicant. This equates to 36% (2.24) higher pH and 2357% (1.65 mg/g) higher free nicotine in the VERVE® Discs products tested by STL compared to FDA internal data for chewing tobacco products. However, the estimated free nicotine based on STL's test data is comparable to or lower compared to the levels for General Snus and FDA internal data for dissolvables, moist snuff, and snus **Error! Reference source not found.**tobacco products. Free nicotine is a calculated value and depends on pH and total nicotine. A slight change in pH can significantly impact the amount of free nicotine, which is seen these cases. While pH in smokeless tobacco products is generally controlled, pH is not controlled in VERVE® products. The estimated free nicotine in the VERVE® Discs products is already higher by 1486% compared to chewing tobacco. With the measured pH in VERVE® Discs higher in STL measurements (8.34) than in the applicant submitted measurements ( ), this made the difference in STL's free nicotine even higher (2357%) compared to chewing tobacco. However, this increase in free nicotine does not translate into an increase in addiction liability. The abuse liability aspect of the nicotine levels in the VERVE® products is addressed in section 2.4 of this review.

The toxicology review addressed the potential for nicotine poisoning with the VERVE® products. The applicant contracted studies to assess that the packaging of VERVE® Chews and Discs complied with child-resistant packaging to avoid potential accidental ingestion. The packaging was found to be compliant with the current Consumer Product Safety Commission (CPSC) standards and protocols for poison prevention packaging set forth in the Code of Federal Regulations Title 16, Part 1700. McGuigan (2003) has reported that the pediatric lower limit of lethality is 1 mg/kg nicotine by oral ingestion (5, 6). Mayer et al. (2014) provided an estimate of the fatal dose in adults as 0.5-1 g of ingested nicotine, or a weight-based oral dosage (LD50) of 6.5-13 mg/kg (8, 9) (rounded upward to 7-14 mg/kg; 7, 9). To include children <6 years old in this range, the range was extended to the lower limit of 1 mg/kg, or a final range of 1-14 mg/kg. Ingestion of an entire tube of VERVE® Chews or Discs could result in nicotine intakes of 18 and 24 mg of nicotine, respectively. In a 60 kg adult, ingestion of entire tube of VERVE® Chews and Discs could result in nicotine exposures of 0.3 and 0.4 mg/kg body weight, respectively. Using an estimated child weight for ages 3 to <6 years as 18.6 kg, this could result in exposures of 0.97-1.29 mg/kg body weight (8), assuming 100% absorption of the entire tube of chews or discs which could result in a lethal dose of nicotine to children. However, because nausea and vomiting are early and frequent symptom of nicotine poisoning, it is unlikely that 100% of the nicotine would be extracted through accidental ingestion (10); If a child did ingest an entire tube, the nicotine that would enter the system would likely cause the child to vomit before the entire nicotine dose could be absorbed (10,11). If a child were to consume two VERVE® Chews or Discs, a more likely scenario than ingestion of an entire tube due to the products' child-resistant packaging, this could result in exposure of 3 mg of nicotine or 0.16 mg/kg body weight of nicotine. Given the presence of the child-resistant packaging and the amount

of nicotine available in an entire tube of discs or chews, death from accidental ingestion would be unlikely. In conclusion, it is unlikely that a lethal dose of nicotine would be consumed with VERVE® products by either the intended adult user population or in accidental ingestion in children.

NNK - Over the 12-month testing period, NNK was not detected in the VERVE® Chews products. In VERVE® Discs Green Mint, NNK decreased at 12M by 11% (0.04 ng/portion). Compared to cigarettes (145 ng/g) and General Snus (304 ng/g), NNK measured in VERVE® Discs is greatly reduced (0.74 ng/g; Appendix Table 16)

NNN - Over the 12-month testing period, NNN was not detected in the VERVE® Chews products. In VERVE® Discs Blue Mint there was an increase in NNN of 12-44% (0.05-0.29 ng/portion) at 6M and 12M; in VERVE® Discs Green Mint, there was an increase of 17% (0.21 ng/portion) at 6M. From a chemistry perspective, the 17% increase in NNN (12M, VERVE® Discs Green Mint) also may be due to the variability in the analytical measurements, where the %RSD is 40-55% for NNN (see bolded text in Appendix Table 18). Compared to cigarettes (284 ng/g) and General Snus (1080 ng/g), NNN measured in VERVE® Discs is greatly reduced (0.74 ng/g; Appendix Table 16)

The chemistry review showed (Appendix Tables 15 and 16) that HPHC exposure in the new products can be reduced by 25-100% compared to Nicorette gum, General Snus, and cigarettes (Marlboro 100's Box), except for the arsenic and free and total nicotine, as discussed above. Because the use of the VERVE® products is similar to other smokeless tobacco products, a comparison is also made of the measured HPHC levels in the new products to HPHC levels found in chewing tobacco, dissolvables, moist snuff, and snus (Appendix Table 17). The results indicate that HPHC levels in the new products can be reduced by 2-100% compared to other smokeless tobacco products, except for free nicotine as discussed above. Based on the measured HPHCs in the VERVE® Discs and Chews and the comparator products, nicotine and arsenic are the only HPHCs that increase over time in the Discs or Chews and are higher in comparison to at least one product. Neither the toxicology nor the BCP review identified these increases as a toxicological or abuse liability concern.

2.3.2 Non-Nicotine Ingredients

The applicant submitted information on the non-nicotine ingredients in a TPMF (b) (4) which was reviewed by both the chemistry and the toxicology reviewers. The ingredients are presented in Appendix Table 13. Literature reviews were included to address potential toxicity of the non-nicotine ingredients.

The applicant references the TPMF for the quantitative formulations of all four products. The applicant states that the primary ingredients in all the new products are tobacco-derived nicotine, polymer, non-tobacco cellulose fiber, flavorings, texture modifier, binder, and colorant. These ingredients are composed of materials commonly used in and generally recognized as safe (GRAS) in food products. Although GRAS is not applicable to tobacco products, a consideration of the underlying data used in the assessments for oral exposures to these ingredients can be informative for the toxicological evaluation of ingredients in oral tobacco products, such as in these PMTA Reports. Additionally, the VERVE® Discs products contain a (b) (4)), while the VERVE® Chews products contain an artificial sweetener, (b) (4) .

(b) (4) , is the primary component of the VERVE® Discs products base material and is used for (b) (4) for the Discs pieces. Based on Table 6.1-12 in Section 6.1.3.6.2 of the PMTAs, the VERVE® Discs products contain approximately (b) (4) mg/piece of (b) (4) or 55% by weight relative to the weight of each Disc. Over time, (b) (4)

materials may hydrolyze at excessive temperatures to the corresponding precursor diamines (i.e., 2,4-toluene diisocyanate, 2,4-diamino toluene), which have been reported in animal studies to significantly increase the incidence of tumors in the liver and mammary glands (12-14). Precursor diamines are not expected to be present when this (b) (4) is chewed. The applicant provided gas chromatography/mass spectrometry (GC/MS) analyses of the (b) (4) (see Appendix 7.5.1-125 of the PMTAs) to determine the presence of the precursor diamines and the results show no detectable levels of 2,4-toluene diisocyanate and 2,4-diamino toluene. In medicated chewing gum formulations, elastomers and rubbers are generally present at a range of 15-45% (15). In addition, the safety data sheet indicates that (b) (4) is not carcinogenic as defined by the International Agency for Research on Cancer, the National Toxicology Program, and the Occupational Safety and Health Administration (OSHA); and is also not hazardous under the criteria of the OSHA HaxCom 2012 (see Appendix 7.4.1-129 of the PMTAs; 16). Thus, from a chemistry perspective, the level of (b) (4) in the VERVE® Discs products at 55% by weight ((b) (4) mg/piece) does not raise concerns.

The manufacturer of (b) (4), indicates that this material meets the requirements of the FDA-modified ISO 10993, Part 1 "Biological Evaluation of Medical Devices" tests with human tissue contact time of 30 days or less (17). For example, aromatic polyurethanes based on diphenylmethane diisocyanate (MDI) may hydrolyze and produce methylene dianiline (MDA) and, as such, this needs to be considered in any end-use application. Per the U.S. Agency for Toxic Substances and Disease Registry (18), no data on the oral absorption of MDI are available. However, 84 cases of jaundice occurred following accidental ingestion of MDA in contaminated whole-meal bread in 1965 , but no MDA exposure levels were reported therein (19). WHO reports that the health endpoints of most concern for MDA are occupationally induced respiratory diseases (20). The corresponding precursor diamines (i.e., 2,4-toluene diisocyanate, 2,4-diamino toluene) have been reported in animal studies to significantly increase the incidence of tumors in the liver and mammary glands (21, 14). However, given that precursor diamines are not detectable in VERVE® products, (b) (4) ® as a thermostable base material in the new products is therefore not of toxicological concern.

(b) (4) is commonly used as a binder, emulsion stabilizer, and fixative, and is a homopolymer of (b) (4) (23). (b) (4) is listed as a Group 3 chemical (not classifiable) based on findings of inadequate evidence of carcinogenicity in animals and no available human data (24). FDA permits use of (b) (4) homopolymers and copolymers as components of adhesives, resinous and polymeric coatings, and paper or paperboard when intended for contact with food (21 CFR 172.615). Notably, 21 CFR 172.615 is not applicable to tobacco products. However, consideration of the underlying data used to determine safety for oral exposures to ingredients listed in 21 CFR 172.615 can be informative for the toxicological evaluation of ingredients in oral tobacco products, such as in these PMTA Reports. Further, the ingredients literature review provided by the applicant (Section 7.5.1 of the PMTAs) indicates that a dose of 0.2 ml of 1.25% (b) (4) in ethanol saline did not alter the intact oral epithelium of hamsters in a 6-week study (25). No irritation was reported in human volunteers exposed to a 50% concentration of aqueous polyvinyl solution in an occlusive skin irritation test (26). If the new products were to be accidentally ingested, this would not be of toxicological concern as the (b) (4) ®, and cellulose would not be absorbed in the gastrointestinal tract and would be eliminated via defecation (16, 24).

Together, this evidence indicates that (b) (4) is not of toxicological concern as a base material in the VERVE® products.

(b) (4) is a high-intensity sweetener that is 200-300 times sweeter than sucrose (table sugar). (b) (4)

Miao et al. (27) reported 0.13% of (b) (4) in chewing gum, 0.0076-0.013% in snus, and 0.27-0.82% in

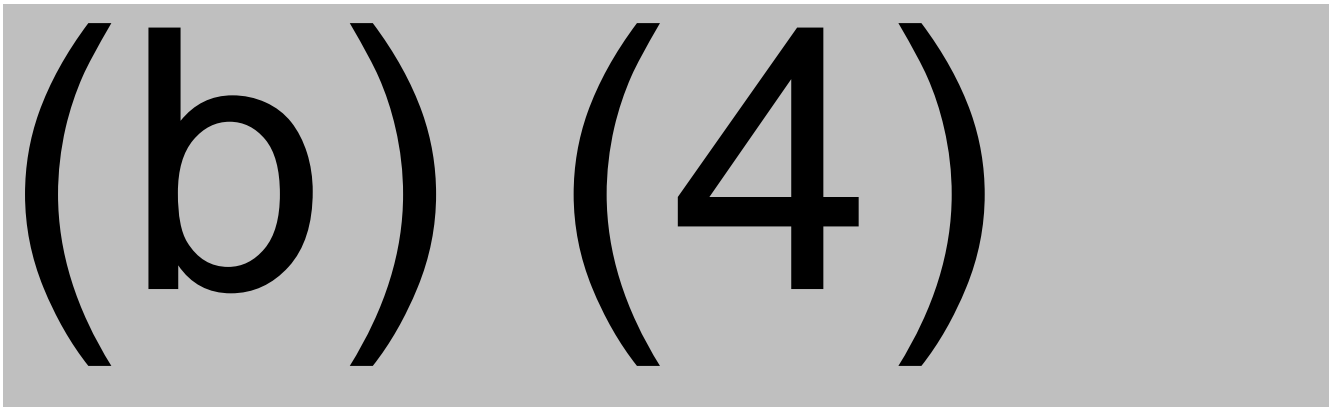
a candy mint lozenge. According to 21 CFR 172.804, the recommended limit for (b)(4) used as an additive is no more than 0.5% by weight of ready-to-bake products or finished formulations, prior to baking. In chewing gum, the level of artificial sweeteners range is 0.05-0.5% by weight. Based on Table 6.1-12 in Section 6.1.3.6.2 of the PMTAs, (b)(4) is present in the VERVE® Chews products at (b) (4) mg/piece (0.15%), which is less than the recommended limit for a food additive in ready-to-bake products or finished formulations, and within the range used in chewing gum and a candy mint lozenge. The highest potential (b)(4) exposure per tube of the new products is (b) (4) mg/person/day or (b) (4) mg/kg bw/day. The estimated potential exposure to (b)(4) from the new products is approximately 62 times lower than the acceptable daily intake (ADI; 40 mg/kg) established by Joint FAO/WHO Expert Committee on Food Additives (JECFA) and 78 times lower than the FDA ADI of 50 mg/kg. Thus, from chemistry and toxicology perspectives, the amount of (b)(4) used in the VERVE® Chews products does not raise a concern.

All of the new products contain menthol characterization flavor in a form of or in combination with either or or both. Based on Table 6.1-12 in Section 6.1.3.6.2 of the PMTAs, small amounts of mg/piece) are used in the VERVE® Chews Blue Mint and VERVE® Chews Green Mint products. According to the TPMF, the total quantity of menthol discussed in this review is the total amount of and menthol weight fraction present in other menthol-containing ingredients. Chen et al., 2010 evaluated 25 sub-brands of mentholated and nonmentholated smokeless tobacco products and the reported menthol levels range from 0.85 to 5.25 mg/g (28). Moreover, Ai et al., 2016 evaluated 45 cigarette products (23 mentholated and 22 nonmentholated) available in the U.S. market and the menthol content in mentholated cigarettes ranges from 3.6 to 16.61 mg/g (2.9 to 19.6 mg/cig; 29). The menthol levels present in the VERVE® Chews Blue Mint, VERVE® Chews Green Mint, and VERVE® Discs Green Mint products are comparable to those reported in all smokeless tobacco products and mentholated cigarettes. However, the VERVE® Discs Blue Mint product contains higher amount of menthol compared to the levels reported in mentholated cigarettes (27%) and smokeless tobacco products (302%). Menthol has the potential to be a permeation enhancer and could increase the uptake of HPHCs. However, as the HPHCs in the VERVE® products are generally lower than selected comparators to represent the current U.S. tobacco market, it is unlikely that the addition of menthol in the VERVE® products presents a toxicological concern.

Ingredients for generation products of the VERVE® Discs Blue Mint

The PMTAs included studies conducted using prototypes or previous-generation products of VERVE® Discs Blue Mint. The applicant provided the CAS number, quantities, and functions for each generation (b) (4), Gen 1, Gen 1A, Gen 2 (VBM-FG2), and Gen 3) of VERVE® Discs Blue Mint in Exhibit #85 of the EIR. As noted in the "additional information" section of the EIR, (b) (4) The Gen 3 product is the current new product referenced as VERVE® Discs Blue Mint in the PMTAs. The EIR also indicated that the difference between (b) (4) and the current VERVE® Discs Blue Mint product is that (b) (4) .

(b) (4)



The chemistry review identified a deficiency in the information on the ingredients as presented in the TPMF. The deficiency is presented in Section 2.2.8 of this review. As TPL, I do not recommend that this deficiency be communicated to the TPMF owner or applicant. Scientific review of the single ingredients and individual components of (b) (4) indicate that none of the ingredients in the new tobacco products are present in amounts that raise toxicological concerns.

2.3.3 Summary of Toxicological Findings

The applicant states that an assessment of the toxicological risks of the non-tobacco ingredients used to manufacture the new products suggest no substantial health risks. USP-grade tobacco-derived nicotine in the new products conveys health risks that are likely comparable to those of NRT gum. The toxicology review provides this summary of key findings:

- The data provided by the applicant for the four VERVE® products do not raise toxicological concerns because of overall reduction of exposure to HPHCs compared to information available for other tobacco products that comprise the current U.S. tobacco market.
- This determination was made in the absence of original toxicology study data; extensive literature reviews, health assessments, and ingredient assessments provided by the applicant support that the VERVE® products will not raise concern from the toxicological perspective.
- Arsenic levels in VERVE® Chews were lower by 51% and 68% than those of comparator smokeless tobacco products with similar daily usage patterns (General Snus and NRT product Nicorette® Gum, respectively).
- Arsenic levels in VERVE® Chews were lower than those of other smokeless tobacco products (chewing tobacco (↓97), dissolvables (↓94), moist snuff (↓95), snus (↓91%)) based on FDA internal data and as calculated in the chemistry review.
- While there was a higher level of arsenic in VERVE® Chews compared to Marlboro 100's Box cigarettes, the highest arsenic exposure level in VERVE® Chews was estimated to be lower (4.0x10-7 mg/kg/day) than USEPA RfD (3.0x10-4 mg/kg/day).
- The non-tobacco ingredients are identified by the applicant as food grade, GRAS, or biocompatible medical grade. Although these designations are not applicable to ingredients used in tobacco products, we note that exposure to these ingredients from use of the new tobacco products is tens to thousands of times lower than the toxicity reference values for these ingredients.
- Based on the underlying toxicity data that support the reference values for these ingredients, there is no toxicological concern.
- Due to minimal HPHC exposure, the new products likely present lower public health concern for tobacco-related diseases than cigarette smoking or other smokeless tobacco products, and the

health effects of the candidate products would likely be similar to those of current NRT products, including nicotine gum.
- If used exclusively instead of smokeless tobacco products, VERVE® products offer the potential for reduction in oral cancer risk. TSNAs, potent tobacco carcinogens, are reduced greater than 100-fold in the new tobacco products compared to cigarettes and smokeless tobacco.
- From a toxicological perspective, the VERVE® Chews and VERVE® Discs PMTAs do not raise concerns with respect to issuing marketing orders for these products.

As TPL, I agree with the toxicology review conclusion. Based on the ingredients and the measured HPHCs in the VERVE® products, if a smoker were to significantly decrease or eliminate their CPD and replace that with the VERVE® products, this would likely present lower public health concern for tobacco-related diseases than cigarette smoking. If a polytobacco user were to switch to the VERVE® products from a smokeless tobacco product, this too has the potential of lower HPHC exposure and lower potential for some tobacco-related diseases. Based on the ingredients and HPHCs, the health effects of the VERVE® products would likely be very similar to those of current NRT products, including nicotine gum.

2.4. Individual Health Impact

2.4.1. Overview of Behavioral and Clinical Pharmacology (BCP) Studies

The applicant submitted two abuse liability studies:

1. Characterization of nicotine exposure profiles and subjective measures of VERVE® Discs products for abuse liability determination in adult smokers relative to combustible cigarettes and nicotine gum
2. Characterization of nicotine exposure profiles and subjective measures of products currently marketed as VERVE® Chews for abuse liability determination in adult smokers relative to combustible cigarettes and nicotine gum

The PMTAs also included a study providing analysis of the subjective measures of withdrawal and direct effects of the product that were obtained from the two studies above:

3. Comparisons of subjective measures on tobacco/nicotine withdrawal and direct effects of product from two clinical studies

The BCP review also evaluated three studies that looked at use patterns of VERVE® products:

4. Six-week actual use study of oral tobacco-derived nicotine products currently marketed as VERVE® Discs and VERVE® Chews
5. VERVE® Discs 12-Week extended home use test Final Report —PowerPoint presentation
6. ALCS In-Market Adult Consumer Study (MACS): Oral tobacco-derived nicotine products currently marketed as VERVE® products

Finally, the BCP review also looked at the applicant's literature review and the applicant's studies of other oral products that were prototypes for the products that are the subject of the PMTAs:

7. A randomized, controlled, parallel group pilot clinical study to determine changes in biomarkers of exposure (BOE) in adult smokers allowed ad libitum VBM-FG2 disc use relative to adult smokers not allowed VBM-FG2 disc use
8. Characterization of plasma nicotine profile from a single-use of two prototype oral tobacco test

products(b) (4) in adult smokers

The general design of the studies reviewed by BCP are provided below. The two abuse liability studies were similar in design, with one evaluating VERVE® Discs and the other evaluating VERVE® Chews.

Characterization of nicotine exposure profiles and subjective measures of VERVE® Discs products for abuse liability determination in adult smokers relative to combustible cigarettes and nicotine gum

Study Products: VERVE® Discs Green Mint, VERVE® Discs Blue Mint (GEN 3; 1.5 mg nicotine); Nicorette Fresh Mint gum nicotine polacrilex gum (2 mg nicotine) and the participant's UB cigarette were reference products.

Study Population: Participants were 28 healthy male (n=19) and female (n=9) adult self-reported exclusive smokers of combusted cigarettes who reported consumption of 10-20 CPD for at least 1 year. Participants were aged 21-65 years and provided a positive urine cotinine test at screening.

Study Design: This study used an open-label, randomized, four-way crossover design to evaluate PK measures, subjective measures, and product use behaviors in response to use of VERVE® Discs Green Mint, VERVE® Discs Blue Mint, subjects' UB cigarettes, and Nicorette gum. The study characterized use behavior of VERVE® Discs and compared nicotine PK profiles and subjective effects of VERVE® Discs with UB cigarettes and Nicorette gum. The study lasted 10 days. Participants were asked to use the nicotine disc products at home on Study Days -6, -5, -4, -3, and -2 as a trial period during which they reported the number of VERVE® Discs and UB cigarettes used per day. They then used the VERVE® Discs, UB cigarettes, and Nicorette gum under controlled conditions in the laboratory on Study Days 1-4, during which PK and subjective measures were collected. Participants used each of the VERVE® products and comparators once, and product order (Study Day) was randomized. In the laboratory, participants smoked one of their UB cigarettes with 10 inhalations at 30-sec intervals, used one VERVE® Disc for 30 min, or "chewed and parked" one piece of nicotine gum for 30 min according to the product's instructions for use. FDA's statistics review included an evaluation of this study and concluded that the linear mixed model used in the analyses was appropriate for the study objectives. The statistics review found that despite differences in the sample size for the study groups, the study was sufficiently powered to detect a range of clinical differences for the PK outcomes at the indicated significance level. The secondary endpoints on subjective measures were analyzed using summary descriptive statistics without statistical comparisons.

Relevant Study Outcomes: Primary endpoints included nicotine C_{max} from blood plasma samples, maximum reduction in subjective Urge to Smoke, and maximum subjective ratings of how pleasant the product was. Secondary endpoints included nicotine T_{max} and AUC from start of product use to 180 min or last measurable concentration (AUC_{0-180}), subjective measures of tobacco/nicotine withdrawal during product use using a visual analogue scale (VAS), maximum reduction in withdrawal from pre- to post-product use, subjective responses to the Direct Product Effects Questionnaire during product use measured using a VAS, maximum responses of Direct Product Effects, subjective responses to the Use the Product Again Questionnaire using a VAS both immediately after product use and 180 min after product use, number of test products used during the trial period, time product was in mouth during the trial period, number of CPD during the trial period, and subjective responses to the modified Cigarette Evaluation Scale (mCEQ) one day before product use.

Characterization of nicotine exposure profiles and subjective measures of products currently marketed as VERVE® Chews for abuse liability determination in adult smokers relative to combustible cigarettes and nicotine gum

Study Products: VERVE® Chews Green Mint, VERVE® Chews Blue Mint (1.5 mg nicotine); Nicorette Fresh Mint gum nicotine polacrilex gum (2 mg nicotine) and the participant's UB cigarette were reference products.

Study Population: Participants were 28 healthy male (n=18) and female (n=10) adult self-reported exclusive smokers of combusted cigarettes who reported consumption of 10-20 CPD for at least 1 year. Participants were aged 21-65 years and provided a positive urine cotinine test at screening.

Study Design: This study used an open-label, randomized, four-way crossover design to evaluate PK measures, subjective measures, and product use behaviors in response to use of VERVE® Chews Green Mint, VERVE® Chews Blue Mint, subjects' UB cigarettes, and Nicorette gum. The study characterized use behavior of VERVE® Chews and compared nicotine PK profiles, nicotine delivery, and subjective effects of VERVE® Chews with UB cigarettes and Nicorette gum. The study lasted 10 days. Participants used the nicotine chewable products at home on Study Days -6, -5, -4, -3, and -2 as a trial period during which they reported the number of VERVE® Chews and UB cigarettes used per day. They then used the VERVE® Chews, UB cigarettes, and Nicorette gum under controlled conditions in the laboratory on Study Days 1-4, during which nicotine PK and subjective measures were collected. Participants used each of the VERVE® products and comparators once, and product order (Study Day) was randomized. In the laboratory, participants smoked one of their UB cigarettes with 10 inhalations at 30-sec intervals, used one VERVE® Chews for 30 min, or "chewed and parked" one piece of nicotine gum for 30 min according to the product's instructions for use. FDA's statistics review concluded that the linear mixed model used in the analyses was appropriate for the study objectives and, despite differences in the sample size for the study groups, the study was sufficiently powered to detect a range of clinical differences for the PK outcomes at the indicated significance level. The secondary endpoints for subjective measures were analyzed using summary descriptive statistics without statistical comparisons.

Relevant Study Outcomes: Primary endpoints included nicotine C_{max} from blood plasma samples, maximum reduction in subjective Urge to Smoke, and maximum subjective ratings of how pleasant the product was. Secondary endpoints included nicotine T_{max} and $AUC_{0\text{-}180}$, subjective measures of tobacco/nicotine withdrawal during product use using VAS, maximum reduction in withdrawal from pre- to post-product use, subjective responses to the Direct Product Effects Questionnaire during product use measured using a VAS, maximum responses of Direct Product Effects, subjective responses to the Use the Product Again Questionnaire using a VAS both immediately after product use and 180 min after product use, number of test products used during the trial period, time product was in mouth during the trial period, number of CPD during the trial period, and subjective responses to the mCEQ one day before product use.

A general summary of the subjective measures study is provided below:

Comparisons of subjective measures on tobacco/nicotine withdrawal and direct effects of product from two clinical studies

Study Products: VERVE® Discs and Chews Green Mint, VERVE® Discs and Chews Blue Mint (1.5 mg nicotine)**;** Nicorette Fresh Mint gum nicotine polacrilex gum (2 mg nicotine) and the participant's UB cigarette were reference products.

Study Design: The secondary endpoints on subjective measures were analyzed using summary descriptive statistics without statistical comparisons. Therefore, a linear mixed model for analysis of variance was used to conduct post hoc analyses to compare responses to the subjective questionnaire

items from the Tobacco/Nicotine Withdrawal and Direct Effect of Product Questionnaires in Study 1 and Study 2 (listed above).

Relevant Study Outcomes: The primary outcomes included maximum reduction in VAS scores (from pre- to post-product use) for previously non-analyzed Tobacco/Nicotine Withdrawal and Direct Effect of Product Questionnaire items. Change scores were compared between the four study products with scores from UB cigarette and Nicorette gum use.

A general summary of the actual use and in-market survey studies are as follows:

Six-week actual use study of oral tobacco-derived nicotine products currently marketed as VERVE® Discs and VERVE® Chews

Study Products: VERVE® Discs Green Mint, VERVE® Discs Blue Mint, VERVE® Chews Green Mint and VERVE® Chews Blue Mint (collectively referred to as VERVE®, except where significant differences in flavor or format are identified). All products contained approximately 1.5 mg nicotine/piece.

Study Population: Current adult cigarette smokers (n=517) of legal age to purchase tobacco[10] up to age 64 years who were not planning to quit in the next 3 months. Participants reported having smoked at least 100 cigarettes in their lifetime and smoking cigarettes "every day" or "some days" in the past 30 days. Participants who also reported current past 30-day use of other tobacco products (i.e., cigars, pipe/hookah, dip/snuff, chewing tobacco, snus pouches, other oral tobacco-derived nicotine products, electronic nicotine delivery systems [ENDS]) were included.

Study Design: A multisite 6-week ambulatory (i.e., at home) observational study of participants who were randomly assigned to receive VERVE® Discs (n=256) or VERVE® Chews (n=261) in Blue Mint and Green Mint varieties. Participants completed a two-day at-home product use trial (Phase 1) during which participants were asked to sample both VERVE® flavor varieties (Blue Mint or Green Mint) for at least 5 min. Participants were invited to participate in Phase 2 of the study if they used the product as instructed during Phase 1, and if, in response to questions regarding whether they intended to use VERVE®, stated they "strongly agree", "agree", "somewhat agree" or "somewhat disagree" with the "Intent to Use" statements.[11] Phase 2 of the study involved 6 weeks of ad libitum extended use of the assigned VERVE® Discs or Chews products. The applicant noted that the data analyses for this observational study were not hypothesis-driven. Therefore, a formal sample size calculation was not conducted. No statistical testing of differences between groups was conducted. Instead, data were analyzed and reported descriptively among the study groups and the total study sample using proportions and frequency distributions.

Relevant Study Outcomes: The primary outcomes during Phase 1 included a) average ratings of liking for each VERVE® product, b) average duration of VERVE® used per occasion (minutes), c) number of VERVE® products used for each variety, d) types and amounts of other tobacco products used each day, and e) CPD, if participants smoked cigarettes that day. During Phase 2, the primary outcomes described participants' use patterns of VERVE® over the 6-week study, including a) number of days per week using VERVE®, cigarettes, and/or other tobacco products, b) amount of VERVE®, cigarettes, and/or other

10. [10] Applicant did not provide a specific age.

11. [11] Statements regarding Intentions to use VERVE®: I would consider using a **VERVE®** [DISC/CHEW] more than once. (6-point agreement scale); I expect to use a **VERVE®** [DISC/CHEW]. (6-point agreement scale); It is likely that I will regularly use **VERVE®** [DISCS/CHEWS] in the next 6 months. (6-point agreement scale); **VERVE®** [DISCS/CHEWS] will be my regular brand of oral tobacco in the next 30 days. (6-point agreement scale)

tobacco products used per week, and c) distribution change in CPD (e.g., decrease, same, increase) from baseline to the end of study. The proportion of participants who a) started using VERVE®, b) used both VERVE® flavor varieties, c) completely stopped using cigarettes and/or other tobacco products, d) started using VERVE® and stopped using cigarettes and/or other tobacco products, or e) started using VERVE® and continued using cigarettes and/or other tobacco products was also evaluated.

VERVE® Discs 12-week extended home use test Final Report—PowerPoint presentation

Study Products: Prior version of VERVE® Discs Blue Mint (Gen 1). The product is a non-dissolvable tobacco-derived nicotine disc products, each piece containing 1.5 mg nicotine.

Study Population: 284 adult cigarette smokers aged 21-54 years. Participants reported "purchase interest in VERVE® Discs."

Study Design: This study measured extended at-home use of a prior version of VERVE® Discs Blue Mint (Gen 1) products. This multi-site study lasted 12 weeks. Study objectives were to understand how adult smokers used Gen 1 VERVE® Discs over time and to compare their product usage relative to cigarettes. Participants initially conducted a trial "disc test" where they reported amount of cigarette and other tobacco product use. For the next 8 weeks, they also reported VERVE® product use. They were given Gen 1 VERVE® Discs to use at home during Weeks 1-8 but were also permitted to use cigarettes and other tobacco products. Daily use of Gen 1 VERVE® Discs was compared to daily use of cigarettes and changes in product acceptance to Gen 1 VERVE® Discs were measured.

Relevant Study Outcomes: Subjective measures of abuse liability were collected, including product acceptance questionnaires with items that measured product acceptability, how the product was used, product liking, and sensory experience from product use. The GEN1 VERVE® Discs contain the same amount of nicotine (1.5 mg/piece) as the current VERVE® Discs Blue Mint product but they do not contain flavor coating and have a modified texture. These changes could impact all the relevant study outcomes (i.e., measured product acceptability, how the product was used, product liking, and sensory experience from product use).

ALCS In-Market Adult Consumer Study (MACS): Oral Tobacco-Derived Nicotine Products Currently Marketed as VERVE® Products

Study Products: VERVE® Discs, VERVE® Chews, VERVE® Melts, VERVE® Chewable Dissolvables.

Study Population: (b) (4)

Study Design: (b) (4)

(b) (4)

Relevant Study Outcomes: (b) (4)

A Randomized, Controlled, Parallel Group Pilot Clinical Study to Determine Changes in Biomarkers of Exposure (BOE) in Adult Smokers Allowed Ad Libitum VBM-FG2 Disc Use Relative to Adult Smokers Not Allowed VBM-FG2 Disc Use

Study Products: Prior Version of VERVE® Discs Blue Mint (Gen 2), referred to as VBM-FG2 in this study. The product is a non-dissolvable tobacco-derived nicotine disc product, each piece containing 1.5 mg nicotine.

Study Population: Healthy male and female adult cigarette smokers aged 21-65 years. Of 154 participants enrolled and randomized in the study, 146 participants completed the study (n=89 test group; n=57 control group). Data for the outcomes presented in all the application's tables denote sample size ranging from n=66-87 participants in the test group and n=43-55 participants in the control group.

Study Design: Randomized, controlled, open-label, parallel group, multi-center, five-week pilot study to determine changes in BOE in adult smokers allowed *ad libitum* (up to 24 discs per day) use of VBM-FG2 discs (test group) relative to adult smokers who were not permitted use of VBM-FG2 discs and continued smoking their UB cigarettes (control group). The study consisted of a one-week baseline period during which all participants smoked their UB cigarettes, followed by a four-week product use period for participants randomized to the test group. Control participants continued smoking their UB cigarettes during the four-week period.

Relevant Study Outcomes: The primary endpoint was the percent change in urinary total 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol (NNAL) from baseline to end of study. Secondary endpoints included percent change in urinary nicotine equivalents (cotinine, trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-O-glucuronide, nicotine-N-glucuronide, and cotinine-N-glucuronide), S-phenylmecapturic acid (S-PMA), blood COHb, exhaled CO, CPD, and Fagerström Test for Cigarette Dependence (FTCD) scores from baseline to end of study. Mean daily consumption of VBM-FG2 discs was also reported.

(b) (4)

Study Products: (b) (4)

Study Population (b) (4)

Study Design: (b) (4)

Relevant Study Outcomes: (b) (4)

(b) (4)

2.4.2. Nicotine Pharmacokinetics

Two Nicotine Exposure Studies

The BCP review of the applicant's two nicotine exposure studies provides PK data for VERVE® Discs and VERVE® Chews. In one study using the VERVE® Discs products, a mixed model analysis of variance conducted by the applicant revealed that the nicotine C_{max} means the VERVE® Discs Blue Mint and Green Mint conditions were each statistically significantly lower than the C_{max} mean for the UB cigarettes condition and the C_{max} mean for the nicotine gum condition. Median T_{max} was 60 min for the VERVE® Discs condition, which was equal to that of nicotine gum, but much longer than participants' T_{max} for the UB cigarettes condition (10 min). Nicotine AUC_{0-180} for each of the VERVE® Discs Blue Mint and Green Mint conditions was statistically significantly lower than the AUC_{0-180} mean for the UB cigarettes condition and the AUC_{0-180} mean for the Nicorette gum condition. All participants used the two VERVE® products and Nicorette gum for at least 30 min per product.

The mean values of nicotine T_{max} were reported without statistical comparisons or significance levels. In this study, nicotine PK data were collected only when participants used the VERVE® products and the comparators one time each under controlled use (instructed) conditions, limiting the generalization of the findings on nicotine exposure; real-world use of VERVE® Discs Green Mint and Blue Mint would not involve controlled conditions.

Despite the limitations noted above, the BCP review concluded that based on findings from this study, which compared nicotine PK of the VERVE® Discs products to those of UB cigarettes and Nicorette gum, the VERVE® Discs products are associated with lower abuse liability than UB cigarettes. Although the data collected in this study do not reflect real-world use of the products tested, the nicotine PK data provide valid measures of abuse liability for those products.

A second study looked at the PK of the VERVE® Chews products. Nicotine C_{max} for VERVE® Chews Blue Mint and Green Mint was statistically significantly lower than C_{max} for UB cigarettes, and slightly higher but not statistically significantly different than the C_{max} for Nicorette gum. T_{max} came much later for the VERVE® Chews (at about 45 min) compared to the UB cigarettes (11 min), and somewhat earlier than the Nicorette gum (54 min) (no statistical comparisons reported). Nicotine AUC for VERVE® Chews Blue Mint and Green Mint was statistically significantly lower than that of UB cigarettes, and not statistically significantly different than the AUC of Nicorette gum.

As with the study on the VERVE® Discs, the T_{max} were reported without statistical comparisons or significance levels. In this study, nicotine PK data were collected only when participants used the VERVE® products and the comparators one time each under controlled use (instructed) conditions, limiting the generalization of the findings on nicotine exposure; real-world use of VERVE® Chews Green Mint and Blue Mint would not involve controlled conditions.

Despite the limitations, as stated above regarding the VERVE® Discs, the BCP review concluded that based on findings from this study, which compared PK of the VERVE® Chews products to those of UB cigarettes and Nicorette gum, the VERVE® Chews products are associated with lower abuse liability than UB cigarettes. Similar to the study with the VERVE® Discs products, the data collected in this study do not reflect real-world use of the products tested, but the nicotine PK data provide valid measures of abuse liability for those products; there is lower likelihood of abuse associated with the slower speed of nicotine delivery compared to UB cigarettes.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2.4.3 Behavioral Pharmacology

2.4.3.1. Abuse Liability

Data on NRT gum from the literature were extrapolated to VERVE®, given that the applicant submitted studies to support that abuse liability and nicotine PK are comparable between NRT gum and VERVE® products (Section 3.1). The applicant also provided studies comparing NRT gum to NRT lozenges and data on abuse liability of dissolvable tobacco products. Studies in cigarette smokers and smokeless tobacco users were included.

Applicant's Submitted Studies

The BCP review evaluated studies with data related to the abuse liability of VERVE® Discs and VERVE® Chews in Blue Mint and Green Mint flavors and comparator products. Such data included, but were not limited to: PK parameters measuring plasma nicotine levels during product use (i.e., C_{max}, T_{max}, and AUC), measures of product use (i.e., number of products used per day, amount of use, frequency of use, duration of product use, other product use topography parameters), subjective responses to product use (i.e., self-reported questionnaire responses about urge to use a product, symptoms of nicotine withdrawal, product liking, sensory effects from product use), and data related to BOE (e.g., nicotine and metabolites, total NNAL).

The applicant-submitted studies on VERVE® products, as noted in Section 2.4.1 of this review, include three abuse liability studies assessing VERVE® Discs and VERVE® Chews. As one study used expired Nicorette gum, the applicant repeated the study. The BCP review only addresses the repeated study with fresh Nicorette gum. The abuse liability studies were reviewed to evaluate the PK profiles of and subjective responses after use of VERVE® Discs and/or Chews in smokers. The applicant submitted two additional analyses to further evaluate outcomes from its VERVE® abuse liability studies. The applicant states that the secondary endpoints on subjective measures in its two abuse liability studies using VERVE® products were analyzed using summary descriptive statistics without statistical comparisons. To make additional comparisons between products, the applicant conducted post hoc analyses on items from the Tobacco/Nicotine Withdrawal and Direct Effect of Product Questionnaires. The BCP review also includes an assessment of three studies, two actual use studies and the in-market survey study, to evaluate patterns of actual use of VERVE® Discs and/or Chews among consumers.

The two studies that measured PK data from the VERVE® Discs and the VERVE® Chews also included subjective measures of abuse liability. Maximum Reduction in Urge from pre- to post-product use was smaller from use of VERVE® Discs Blue Mint and Green Mint, but not statistically significantly different, than Maximum Reduction in Urge from use of UB cigarettes or Nicorette gum. In the VERVE® Discs Blue Mint and Green Mint conditions, mean ratings for the "Is the product 'pleasant' right now?" item on the Direct Effects of Product Questionnaire were each statistically significantly lower than mean ratings from the same question in the UB cigarette condition, and were not statistically significantly different than mean ratings from the same question in the Nicorette gum condition. All participants used the two VERVE® Discs products and Nicorette gum for at least 30 min per product. Based on findings from this study, which compared nicotine PK and subjective measures of abuse liability of the VERVE® Discs products to those of UB cigarettes and Nicorette gum, this BCP review concluded that the VERVE® Discs products are associated with lower abuse liability than UB cigarettes and Nicorette gum. Although the data collected in this study do not reflect real-world use of the products tested, the nicotine PK data from a controlled study design provides valid measures of abuse liability for these products.

The study with the same design but using the VERVE® Chews products showed that Direct Product Effects ("pleasantness" item) for the VERVE® Chews were statistically significantly lower than those of UB cigarettes and not significantly different from those of Nicorette gum. Based on findings from this study, which compared PK and subjective measures of abuse liability of the VERVE® Chews products to those of UB cigarettes and Nicorette gum, we conclude that the VERVE® Chews products are associated with lower abuse liability than UB cigarettes and a similar abuse liability to Nicorette gum. Although the data collected in this study do not reflect real-world use of the products tested, the nicotine PK data from a controlled study design provide valid measures of abuse liability for these products.

The applicant then conducted a post-hoc analysis of the secondary endpoints of subjective measures from the two studies discussed above. The BCP review noted that UB cigarette smoking produced a statistically significantly greater maximum reduction in VAS scores on the Tobacco/Nicotine Withdrawal items than use of both flavors of VERVE® Chews. UB cigarette use produced a statistically significantly greater maximum reduction in VAS scores for the "Difficulty Concentrating" item on the Tobacco/Nicotine Withdrawal Questionnaire than use of VERVE® Discs Blue Mint. UB cigarette use produced a statistically significantly greater maximum reduction in VAS scores for all but one item on the Direct Effects of Product Questionnaire compared to use of both flavors of VERVE® Chews. UB cigarette use produced a statistically significantly greater maximum reduction in VAS scores on multiple items of the Direct Effects of Product Questionnaire compared to use of both flavors of VERVE® Discs. UB cigarette use produced a statistically significantly greater maximum reduction in VAS scores for all Direct Effect of Product Questionnaire items compared to Nicorette gum use. Use of Nicorette gum did not statistically significantly reduce withdrawal or direct effects any better than use of VERVE® Discs or Chews. The statistics review identified violations in the assumptions made while using a linear mixed model to conduct this post hoc analysis. Plots of the subject measure residuals against the predicted values exhibited increasing variability as the predicted means increased, which is an indication that the constant error variance assumption may be invalid. Four subjective measures showed deviations from the model assumptions: $E_{\text{max-diffconc}}$ "Difficulty Concentrating", $E_{\text{max-anxious}}$ "Anxious," $E_{\text{max-sick}}$ "Is the product making you feel 'Sick' right now?" and $E_{\text{max-hunger}}$ "Is the product reducing your 'Hunger' for food right now?" Taking these violations into consideration, the statistical review could not confirm the conclusion provided in the post hoc statistical analysis report that the VERVE® products, as well as NRT, did not statistically significantly reduce withdrawal or direct effects compared to UB cigarettes.

The subjective ratings assessed in this analysis reveal that participants' UB cigarettes reduce nicotine withdrawal and improve direct effects of product use (such as satisfaction, calmness, and feeling sick) in smokers better than VERVE® Discs and Chews. These findings suggest that the abuse liability of VERVE® Discs and Chews is lower than the abuse liability of participants' UB cigarettes. Effects were comparable between VERVE® Discs and Chews and Nicorette gum, suggesting that abuse liability for VERVE® Discs and Chews is similar to Nicorette gum. However, based on the statistics review regarding the violations in the assumptions made while using the linear mixed model, these conclusions cannot be confirmed. As such, the BCP review relies on the descriptive statistics provided in the two nicotine PK and subjective measures studies to support conclusions on subjective measures for VERVE® Discs and Chews compared to UB cigarettes and Nicorette gum. As noted already, the results of these two studies support that the VERVE® products have lower abuse liability than UB cigarettes and a similar abuse liability to Nicorette gum.

Literature Review

Overall, findings from the applicant's literature review support that, compared to UB cigarettes and high nicotine content smokeless tobacco, abuse liability of oral tobacco products is low and comparable to that of NRT products (gum or lozenge). These findings are based on nicotine PK profiles and subjective

ratings (e.g., likeability, ability to relieve withdrawal and craving) of oral tobacco products compared to UB cigarettes.

Early studies that assessed PK data in oral NRT products measured blood nicotine concentrations in smokers who used 2 mg or 4 mg nicotine gum. Findings revealed that chewing 2 mg nicotine gum (polacrilex) and 4 mg nicotine gum produced lower nicotine delivery and slower nicotine absorption than cigarette smoking, with the 2 mg nicotine gum resulting in lower nicotine intake than the 4 mg nicotine gum (30). Additional findings revealed that both the 2 and 4 mg nicotine gum produced higher plasma nicotine concentrations at multiple time points during product use compared to a placebo, and a decrease in plasma nicotine concentrations in smokers who switched to 2 mg, but not 4 mg, nicotine gum (31). Further studies on nicotine gum show dose-related increases in serum cotinine levels; blood cotinine concentrations rise with nicotine dose (32, 33). In addition, allowing nicotine lozenges to dissolve produced higher nicotine exposures than immediately chewing and swallowing the lozenge, or chewing the lozenge and then holding it in one's mouth for 5 minutes before swallowing. Comparisons between nicotine gum and lozenge (both 2 mg nicotine content) found that nicotine concentrations associated with use were similar, but the gum's nicotine absorption rate was slower (34). Additional studies have shown that frequency of nicotine product use can also affect nicotine delivery (35), and that nicotine from mouth spray is absorbed faster than a nicotine lozenge or gum (36).

PK findings from studies with non-NRT products similar to the VERVE® products reveal that smokers who are non-oral tobacco users who chewed a 2012 version of VERVE® (1.5 mg/g nicotine) following cigarette abstinence showed smaller, though not significant, increases in plasma nicotine concentrations than non-oral tobacco users who did not abstain (37). Additionally, in a study where several newer smokeless tobacco products, including Ariva, Revel, Stonewall, and Copenhagen moist snuff, were compared to a nicotine lozenge, the nicotine lozenge produced a higher nicotine C_{max} compared to the Stonewall, Ariva, and Revel products (38).

Therefore, PK studies on NRT products reveal that chewing nicotine gum produces lower blood nicotine levels and a slower absorption rate of plasma nicotine than smoking cigarettes. PK studies comparing nicotine lozenges with nicotine gum also find that these products produce comparable nicotine exposure, although nicotine lozenges have a faster nicotine absorption rate. Studies report that moist snuff delivers more nicotine than nicotine lozenges, and newer smokeless tobacco products deliver less nicotine than lozenges.

Oral NRT products are associated with low ratings of pleasantness across products, including nicotine gum and nicotine lozenges. Higher nicotine content gum and lozenges received decreased ratings of acceptability and liking; never smokers and former smokers preferred lower doses of nicotine in gum. Young adults and never smokers appear to have a greater aversion to oral nicotine products and are less likely to experience psychological reward (Section 2.4.3.4).

Studies comparing product acceptability as a measure of the abuse liability of oral tobacco products in smokeless tobacco users show that snuff was rated highest in psychological reward and aversion compared to VERVE® chewable discs, dissolvable tablets, and snus (Section 2.4.3.4). Findings from this literature review conclude that VERVE® Discs have a low abuse liability.

2.4.3.2. Use Behavior and Topography

In the 6-week actual use study, the participants were asked how they used the VERVE® products during a typical use session and where in the mouth they typically placed the product (topography). For VERVE® Discs at Week 1, the majority of participants reported chewing the discs half the time and

letting them rest in the mouth the other half. After Week 1, use patterns were equally divided, where an approximately equal number of participants reported chewing the product most of the time, letting the product rest in the mouth most of the time, or chewing the product half the time and allowing the product to rest in the mouth the other half. Alternatively, for VERVE® Chews, throughout the 6-week use trial, the majority of participants reported chewing the product most of the time. Only 5-8% of participants reported letting the product rest in the mouth most of the time. For both product varieties, overall, an equal number of participants reported typically using the product in the same area of the mouth or typically using the product in different areas of the mouth.

The in-market survey study also collected topography data (i.e., minutes in mouth, placement in mouth, how typically used in mouth). Overall, 38% of current VERVE® product users report using VERVE® while also using another tobacco product (e.g., smoking a cigarette with a VERVE® product in their mouth). Among current VERVE® Discs users, 39% kept the product in their mouth for 10-19 minutes, and 32% used the product for 5 minutes or less. The majority (54%) of participants chewed the discs half the time and let them rest in their mouth the other half, 19% chewed the disc most of the time, and 27% reported letting the product rest in the mouth. Among users who did not chew the disc, 39% rested the product between the lower lip and gum, and 36% kept the product somewhere else in their mouth. Among VERVE® Chews users, 53% kept the product in their mouth for 10-19 minutes, and 22% used the product for 5 minutes. Forty-four percent of participants chewed the VERVE® Chews most of the time, while 34% chewed the product half the time and let them rest in their mouth the other half. Twenty-two percent let the product rest in the mouth most of the time.

2.4.3.3. Product Use/Consumption

The in-market survey study provided product use information. The BCP review noted that all current VERVE® users reported past 30-day use of any VERVE® product plus two or more other tobacco products. Current VERVE® users reported using VERVE® Discs and VERVE® Chews, on average, 13 and 11 days out of the past 30 days, respectively.

For current VERVE® Discs use in the past 30 days, the largest percentage of participants (37%) reported using the product 10-14 days; 7% reported using the product 1-2 days, and 10% reported using the product on all 30 days. Most participants (63%) reported using fewer than five discs per day, 25% used 5-9 discs per day, and 12% averaged 10 or more discs per day. Sixty-eight percent of current users typically used one VERVE® Discs per use occasion and 29% used two VERVE® Discs per use occasion. Two percent of participants reported using three or more discs at the same time.

For current VERVE® Chews use in the past 30 days, the largest percentage of participants (31%) reported using the product 10-14 days, followed by 22% who reported using the product 3-5 days, and 3% reported using the product either 1-2 days or all 30 days. Similar to VERVE® Discs, most (63%) current past 30-day users of VERVE® Chews reported averaging fewer than five VERVE® Chews per day, 25% reported using 5-9 chews per day, and 13% averaged 10 or more chews per day. Fifty-six percent reported typically putting one VERVE® Chews in their mouth during each use occasion, and 34% used two chews during each use occasion. Nine percent reported using three or more chews at the same time.

Almost all (92%) current VERVE® product users also reported currently smoking cigarettes. On average, participants smoked on 24 of the past 30 days, and smoked an average 16 CPD. The frequency and amount of cigarette smoking among VERVE® product current users was comparable to participants who reported ever trying, but not currently using, VERVE products (80% smoked in the past 30 days, average 26 days smoking out of 30 days, average 15 CPD), and among participants who currently

smoked cigarettes, but had never tried an oral tobacco product (86% smoked in the past 30 days, average 26 out of 30 days, average 15 CPD).

Fifty-one percent of current VERVE® product users reported smoking fewer CPD since starting VERVE®, while 38% reported no change in smoking behavior. Eleven percent reported an increase in smoking behavior since starting VERVE®.

Other past 30-day tobacco product use among current VERVE® product users also included cigars (82%), pipe tobacco or hookah (60%), snus pouches (56%), chewing tobacco (42%), dip/snuff (56%), and refillable END products (92%). The applicant notes that due to sample sizes of less than 20 participants for use of some tobacco products among past VERVE® triers and the reference group (current tobacco users who never tried oral tobacco products), the available sample limited the number of comparisons that could be made to three tobacco products (cigars, dip/snuff, and refillable ENDS). Current VERVE® product users who smoked cigars reported smoking on average 9 of the past 30 days, with 53% reporting less than one or more cigars smoked per day on days smoked. Nineteen percent of current VERVE® product users reported smoking five or more cigars per day on days smoked. Current VERVE® product users who used dip/snuff reported using on average 13 of the past 30 days, with 55% reporting using dip/snuff three or fewer times per day on days used. Current VERVE® product users who used refillable ENDS reported using on average 13 of the past 30 days, with the average of amount of use being less than one or 1-2 mL of e-liquid on days used.

Thirty-eight percent of current VERVE® users reduced their amount and frequency of other tobacco use (aggregated for all non-cigarette tobacco products), while 47% reported no change in their use of other tobacco products. Fifteen percent reported using greater amounts or more frequent use of other tobacco products since initiating VERVE® product use.

2.4.3.4. Craving, Withdrawal, and Dependence

The applicant addressed craving, withdrawal, and dependence primarily with literature and the use of oral NRT, smokeless tobacco, and other oral tobacco products.

The two studies that looked at nicotine PK and subjective measures included subjective measures of tobacco or nicotine withdrawal during product use using a visual analogue scale (VAS) and maximum reduction in withdrawal from pre- to post-product use. The BCP review concluded from these studies that the subjective measures indicate lower abuse liability with the VERVE® products than UB cigarettes. The post hoc analysis study also indicated that the VERVE® products, as well as NRT, did not statistically significantly reduce withdrawal or direct effects compared to UB cigarettes. However, as noted earlier, the statistics review noted violations in the assumptions made in this analysis.

Overall, findings from the applicant's literature review support that, compared to UB cigarettes and high nicotine content smokeless tobacco, the abuse liability of these oral tobacco products is low, and comparable to that of NRT products (gum or lozenge). These findings are based on nicotine PK profiles and subjective ratings (e.g., likeability, ability to relieve withdrawal and craving) of oral tobacco products compared to UB cigarettes.

The abuse liability of nicotine gum has also been assessed using subjective measures. Withdrawal symptoms during abstinence appear not to worsen as duration (1 vs. 3 months) of nicotine gum use increases, implying low abuse liability (39). Additional evidence that nicotine gum possesses low abuse liability comes from subjective reports of satisfaction and dependence, which were not higher in

nicotine gum users compared to those who used nicotine patches, inhalers, or sprays (40). Furthermore, ratings of liking from use of 2 mg and 4 mg nicotine gum did not differ (41).

Studies generally have found that for smokers, smokeless tobacco and oral tobacco products are not as desirable as cigarettes and are less effective than cigarettes at reducing craving and withdrawal (42 - 45). For example, Blank and Eissenberg (44) evaluated toxicant exposure and subjective effects in 21 smokers who used potentially reduced exposure tobacco products. In this study, Camel Snus and Ariva both had lower acceptability among smokers compared to UB cigarettes. Both of these smokeless tobacco products were rated as significantly less pleasant and less satisfying than UB cigarettes and did not taste as good. Camel Snus and Ariva were also less effective at relieving smoking urges across the five-day study. Subjective ratings of VERVE® are lower for liking (37) and in ratings of psychological reward and aversion compared to Skoal snuff (46).

The literature review included nicotine PK studies evaluating nicotine delivery from multiple oral tobacco products from a number of clinical trials and population surveys that examine product use behaviors and measures of dependence from oral NRT use. Long-term (greater than 3 months) use and dependency on NRT gum is not common, and the risk of abuse or dependence on oral NRT products is low. Few studies evaluate the abuse liability of VERVE® and dissolvable tobacco products; however, studies support that subjective ratings of these products are low among smokers.

(b) (4)

2.4.3.5. Cessation

The applicant's in-market survey and literature review indicate a low likelihood of former smokers relapsing to tobacco use with VERVE® or other oral tobacco products. The in-market survey evaluated the percentage of VERVE® product ever triers who had been former tobacco users and then relapsed to using the tobacco product they had quit. No VERVE® product ever triers reported re-initiating cigarette smoking after first trying a VERVE® product. Two percent of VERVE® product ever triers reported re-initiating to another tobacco product (other than cigarettes and VERVE®) after first trying a VERVE® product.

The in-market survey also indicates that 4-5% of VERVE® ever triers quit using all tobacco products after trying VERVE® products; however, it cannot be determined whether VERVE® was the catalyst for tobacco product cessation. A study in the literature review indicates that 20-25% of smokers interested in quitting smoking maintain use of oral tobacco products instead of quitting cigarettes (48); however,

12. [12] Percent change from baseline = study group + random error

13. [13] Change from baseline = study group + random error

participants were instructed on how to use the oral tobacco products to assist with quitting smoking and it is unclear whether consumers would normally initiate these non-NRT products with the intent of quitting smoking. Given that the consumer population most likely to initiate VERVE® use is current smokers who also use one or more other tobacco products and that VERVE® products will not be marketed as cessation products, it is unlikely that smokers who are interested or motivated to quit smoking would initiate VERVE® for this purpose. However, based on the BOE data provided and bridging data on HPHCs present in VERVE® Discs and Chews compared to other tobacco products (Appendix Tables 16 and 17), if consumers quit smoking but continue use of VERVE® products, exposure to many HPHCs, including nicotine, CO, COHb, and other non-nicotine BOE, would be significantly reduced compared to smoking cigarettes.

The literature review included studies of non-NRT oral nicotine tobacco products and the likelihood of cessation among current smokers who try these products. Because the intended purpose of NRT products is to assist with tobacco cessation, and the new PMTA products are not tobacco cessation products, it is unclear how the information from NRT cessation studies can be extrapolated to likelihood of cessation using non-NRT products; data for NRT products were not extrapolated to cessation outcomes for VERVE®. While some studies included use of NRT products as comparators to oral tobacco products, studies that focused solely on likelihood of cessation from use of NRT were not included in the BCP review. The applicant states that the literature indicates the proportion of users who continued to use non-NRT products instead of quitting was greater than what was observed for most NRT studies. This finding is consistent with how non-NRT products are marketed. Given these differences in marketing that contribute to differences in use behavior, studies of continued use of NRT products after quitting smoking were not extrapolated to VERVE® products for this review.

The applicant provided summaries of studies that examined the effects of dissolvable tobacco and other smokeless tobacco products on tobacco cessation. In a study of smokers not interested in quitting (n=31), participants were randomized to groups receiving Ariva or Stonewall smokeless tobacco spit-free tobacco lozenges for 2 weeks or a control group that continued to smoke for 2 weeks (47). Participants who used Ariva or Stonewall reported 40% reductions in CPD over the two-week study; however, there were no significant changes in exhaled CO during the two-week period. There were also no changes in withdrawal or craving during the 2 weeks, an effect likely attributable to the fact that participants dual-used cigarettes and oral tobacco products during the study (as opposed to switching completely). Readiness to quit smoking in the next 30 days and within the next 6 months significantly increased among participants who were using the dissolvable products compared to participants who continued to smoke during the two-week study. Specifically, 53% of participants using dissolvable products reported being more motivated to quit, 37% did not change quit intentions, and 11% reported being less likely to quit smoking (47).

Hatsukami et al. (48) evaluated preferences for five different oral tobacco products varying in nicotine content (General Snus, Camel Snus, Marlboro Snus, Stonewall, Ariva) during a two-week cessation trial among smokers interested in quitting (n=99). Participants were blinded to the snus brands but not oral lozenges. During a two-week sampling phase, participants received instructions on how to use the different types of oral tobacco products and instructions for which products to use on a specified day, including time frames during the day for when they should use the oral tobacco products (i.e., use at least three pouches/lozenges prior to 1 pm) and when they could smoke their UB cigarettes, if desired (i.e., after 1 pm). At the end of the two-week sampling phase, participants were instructed to quit smoking and use the oral tobacco product of their choice for an additional 2 weeks. Findings indicate that Camel Snus users had higher cigarette abstinence rates than Ariva or Stonewall users. This effect was likely due to the higher nicotine content in Camel Snus. At the end of the study, participants who used Ariva were significantly more likely to relapse to smoking than participants who used Camel Snus.

Four weeks after the study ended, 25% (Ariva), 20.8% (Stonewall), 48.2% (Camel Snus), and 17.4% (Marlboro Snus) of participants continued to use the oral tobacco products instead of quitting all tobacco products. It was not reported whether these participants switched completely to oral tobacco products or also continued to smoke cigarettes. Because participants were instructed on how to use the oral tobacco products to assist with quitting smoking, the patterns of use in this study may not be applicable to actual use. Given that these oral nicotine products are not smoking cessation therapies, it is also unclear whether consumers would normally initiate these products with the intent of quitting smoking.

Similarly, Borland et al. (43) completed two pilot studies in the United Kingdom (UK) (n=34) and in Australia (n=29) designed to assess the feasibility of offering smokers alternative nicotine products to consider for use in quitting smoking or as a long-term substitute for cigarettes. Participants who were interested in alternatives to smoking cigarettes (UK) or who were respondents in a survey about the harms of smoking (Australia) were provided with boxes of nicotine-containing products (in the UK: NiQuitin CQ lozenge, Oliver Twist; in Australia: Nicobate lozenge, Catch Swedish Snus, Oliver Twist, Stonewall and/or Ariva) and were told to use the products if they wanted to, and either to reduce their smoking or try to quit smoking. Participants in Australia were contacted after one week for follow-up. The length of time that participants sampled the product in the UK was not specified. In the UK, three participants quit smoking during the study; none of the participants used non-NRT products to assist with quitting. Forty-four percent of participants who used non-NRT oral tobacco products thought the products were “possibly good enough” or “good enough” to replace smoking. Similarly, three participants in Australia reported that they had quit smoking at the end of the week. Views of the individual products varied significantly for acceptability as a smoking replacement, with non-NRT as a smoking substitute being less favorable than the NRT lozenge.

The limited evidence suggests that some smokers (approximately 20-25%) who are interested in quitting smoking may switch to and continue to use oral tobacco products instead of quitting all tobacco; however, initiating non-NRT oral tobacco products to quit smoking is influenced by smoker perceptions of whether non-NRT oral tobacco products are similar to NRT products, and the smoker population most likely to initiate oral tobacco product use is unlikely to be current smokers who are interested in quitting. In general, smokers are unlikely to quit smoking or quit all tobacco products through use of non-NRT oral tobacco products.

2.4.4 Summary of Overall Behavioral and Clinical Pharmacology Findings

The BCP review concluded that the PMTAs do not raise concerns about issuing marketing orders from BCP’s perspective.

Based on the applicant’s submitted clinical studies, VERVE® Discs and Chews in Blue Mint and Green Mint flavors are associated with lower plasma nicotine concentrations and lower positive subjective ratings compared to UB cigarettes, reducing their abuse liability and likelihood of use for youth, non-smokers, and former smokers.

- Current smokers who also use one or more other tobacco products are the consumer population most likely to try VERVE® products. The data and literature review submitted by the applicant suggest that smokers who completely switch to VERVE® products or reduce their CPD by 60% or more upon initiating oral tobacco products may significantly reduce their exposure to nicotine and other non-nicotine BOE. However, low subjective appeal and increased craving and withdrawal may prevent current smokers from fully transitioning to VERVE® products. Data from the applicant’s submitted studies suggest that few smokers (11%) switch completely to VERVE® or other oral

tobacco products, but these data are based on one week of use and do not reflect the measured decline in VERVE® acceptability among smokers that was captured in the applicant's 12-week actual use study. Therefore, the percentage of complete switching would likely be lower than the identified percentage in the applicant's study. Dual/poly use is the primary use behavior. Smokers who dual use VERVE® products with cigarettes and do not substantially reduce their CPD (i.e., by 60% or greater) do not reduce their exposure to nicotine or non-nicotine BOE. However, even a modest reduction in daily cigarette consumption may reduce the risk of tobacco related disease due to a decreased exposure to HPHCs.

As TPL, I agree with the BCP review conclusions that there is reduced abuse liability with the VERVE® products compared to cigarettes and a similar abuse liability compared to nicotine gum. There is evidence that a small number of cigarette users might transition to VERVE® products only. Data evidence from a six-week pilot study demonstrate that some cigarette users might decrease their CPD, with a small chance of some decreasing CPD by over 50%. Further, 12-week Extended Home Use data show a consistent average CPD reduction of 32-44% (14.9 vs ≤ 10.2 CPD) concomitant with use of VERVE® prototype products (5-6 discs/day) for the duration of the study. However, the design of the 6- and 12-week actual use study is not the same as real-world use and over time there is decreased appeal of the products. I also agree with BCP conclusions that the low appeal of the VERVE® products over time may impact any smokers transitioning away from cigarettes should the products be introduced into the commercial U.S. tobacco market.

2.4.5 Biomarkers of Exposure (BOE)

The BCP review included an evaluation of BOE data, which was obtained from the applicant's study with VBM-FG2 (*A Randomized, Controlled, Parallel Group Pilot Clinical Study to Determine Changes in Biomarkers of Exposure (BOE) in Adult Smokers Allowed Ad Libitum VBM-FG2 Disc Use Relative to Adult Smokers Not Allowed VBM-FG2 Disc Use*). This study did not use the PMTA VERVE® products but instead used a prior version of VERVE® Discs Blue Mint (Gen 2). The Gen 2 VERVE® Discs contain the same amount of nicotine (1.5 mg/piece) as the current VERVE® Discs Blue Mint product but they do not contain flavor coating. Based on the format (i.e., disc, chew, or prototype), nicotine content, and use behaviors of VBM-FG2, BCP extrapolated these data to inform conclusions on VERVE® products. In this study, the applicant measured BOE in adult smokers, with the test group allowed ad libitum VBM-FG2 and the control group not permitted to use VBM-FG2 but to continue smoking their UB cigarettes. The primary endpoint was the percent change in urinary total NNAL from baseline to end of study. Secondary endpoints included percent change in urinary nicotine equivalents (cotinine, trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-O-glucuronide, nicotine-N-glucuronide, and cotinine-N-glucuronide), S-phenylmecapturic acid (S-PMA), blood COHb, and exhaled CO.

Cigarette smokers who used VBM-FG2 discs for 4 weeks smoked approximately 20% fewer CPD than UB cigarette smokers and may have had significant reductions in COHb. Despite modest reductions in CPD, total NNAL, TNE, S-PMA, and exhaled CO were not significantly different between study groups. Overall, these findings indicate that the majority of smokers dual use VBM-FG2 discs, and do not substantially reduce CPD or their exposure to nicotine or non-nicotine BOE.

The applicant-submitted literature relevant to BOE is summarized below.

2.4.5.1 Effect of Switching to Oral Tobacco Products on BOE

Nicotine BOE

As previously noted, the applicant submitted one study with BOE, the study with VBM-FG2, - a prior version of VERVE® Discs Blue Mint (Gen 2). The Gen 2 VERVE® Discs contain the same amount of nicotine (1.5 mg/piece) as the current VERVE® Discs Blue Mint product but they do not contain flavor coating. While this is not one of the PMTA VERVE® products, the BCP review noted that extrapolating from VBM-FG2 to the VERVE® products was possible. While the non-nicotine BOE of NNAL was the primary endpoint of this study, secondary endpoints included percent change in urinary nicotine equivalents (cotinine, trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-O-glucuronide, nicotine-N-glucuronide, and cotinine-N-glucuronide). For secondary outcomes, there was no significant difference in percent change from baseline in mean nicotine equivalents between study groups. Similar results were observed for analyses of absolute change. At Visit 6, there was a significant difference between groups (p=0.035), with a greater increase from baseline in total nicotine equivalents (TNE) in the control group compared to the test group. There was no significant difference between groups in nicotine equivalents at any other time point.

The applicant-submitted literature review presented studies on nicotine and tobacco BOE from use of NRT products (gum and lozenges) and oral tobacco products (e.g., snus, dissolvables).

Findings regarding the effects on BOE in cigarette smokers who switch to oral nicotine products suggest that many BOE, including nicotine, are reduced in smokers who switch to oral tobacco products; however, among smokers, dual or poly use is the predominant use pattern for oral tobacco products. Compared to exclusive cigarette users, BOE are not significantly reduced in smokers who dual or poly use oral tobacco products. Given the information regarding the VERVE® products indicating poly use, it is not surprising that the nicotine BOE are not significantly different from the control group of smokers.

If consumers were to switch to only using VERVE® products, or significantly decrease their CPD (by 50-60%), the nicotine BOE would likely be reduced. One study found that, of smokers who switched to oral nicotine products, total cotinine was significantly reduced compared to baseline UB cigarette smoking in smokers (n=49) who switched to Exalt smokeless tobacco, Ariva dissolvables, or NRT lozenges for 2 weeks (45). Urinary cotinine levels were significantly reduced in smokers who used Ariva and Camel Snus compared to smoking UB cigarettes.

The applicant-submitted literature review also presented studies that support the high prevalence of dual use among smokers who use oral nicotine products. Allen et al. (49) evaluated gender differences in response to use of snus or NRT gum in a group of cigarette smokers who were willing to substitute snus or NRT gum for cigarettes over 12 weeks to reduce harm. The prevalence of dual use (i.e., using study NRT gum or snus and smoking cigarettes) was high. Among women during Week 1, 85.9% and 79.5% dual-used NRT gum or snus, respectively. Among men during Week 1, 70.7% and 74.0% dual-used NRT gum or snus, respectively. By Week 12, prevalence of dual use was reduced among women (NRT gum=74.6%, snus=49.2%) and men (NRT gum=43.2%, snus=55.8%).

The applicant's review also provided studies addressing the effects of dual use on BOE. Krauttner and Borgerding (42) conducted a study evaluating consumption patterns and effects on BOE among smokers who switched to Camel Orbs, dual-used, or quit tobacco products completely. Over 5 days in a clinic, healthy smokers (n=133, aged 21-65 years) were assigned to either continue smoking their UB cigarettes, switch completely to Camel Orbs (and use at least five Orbs/day), dual use (i.e., smoke UB cigarettes and consume as many Orbs as desired at any time, but not while smoking), or quit use of all

tobacco products. Plasma and urine samples were collected during the study to assess BOE. The dual use group smoked on average two fewer CPD compared to baseline, and CPD in the dual use group were significantly reduced compared to the UB cigarette-only group. There were no significant differences in smoking topography between the UB cigarette and dual use groups. Smokers who switched to using Orbs only consumed approximately 10 orbs/day and dual users consumed approximately 4 orbs/day. Twenty biomarkers, including TNE, were quantified in 24-hr urine samples and the biomarkers nicotine and cotinine were quantified in blood. Urinary TNE levels did not significantly differ between UB cigarette or dual use groups or from baseline in either group; however, TNE levels were significantly decreased in the Orb-only group compared to baseline and the UB cigarette group.

Overall, these studies suggest that TNE was significantly reduced in cigarette smokers who switch completely to oral tobacco products. However, the majority of individuals who use oral tobacco products are dual tobacco users, and very few smokers switch completely. Therefore, most smokers who use oral tobacco products will likely dual use the products with their UB cigarettes. Dual users often reduce their CPD when using oral nicotine products (42). Smokers interested in using oral nicotine products to significantly reduce, but not quit, smoking may experience significant reductions in BOE, including TNE, depending on the extent to which smoking is reduced. One study suggests that a 60% reduction in CPD translates to significant reductions in TNE. However, in general, smokers who dual use cigarettes and non-NRT oral tobacco products may not experience significant reductions in BOE compared to smoking UB cigarettes, particularly if they do not substantially reduce their CPD upon initiating use of oral tobacco products.

Non-Nicotine HPHC BOE

The applicant-submitted study with BOE -- the study with VBM-FG2, a prior version of VERVE® Discs Blue Mint (Gen 2)-- included non-nicotine BOE as well. The Gen 2 VERVE® Discs contain the same amount of nicotine (1.5 mg/piece) as the current VERVE® Discs Blue Mint product but they do not contain flavor coating. This study indicates that there was no significant difference in percent change from baseline or absolute change from baseline in urinary NNAL levels between the test (+ VBM-FG2) and control (-VBM-FG2) groups. NNAL is a biomarker of TSNA exposure and was the primary endpoint of this study. The applicant also conducted statistical analyses of the proportion of participants in subgroups based on total NNAL. Participants were separated into subgroups of increases or decreases in total NNAL from baseline to the end of study visit. There was no significant difference between groups in the proportion of participants in these subgroups. The applicant notes that there was an increase in NNAL from baseline in both study groups, with a smaller increase in the test group. Secondary endpoints of this study included non-nicotine BOE S-phenylmecapturic acid (S-PMA), blood COHb, and exhaled CO. CPD was also measured as a secondary endpoint.

There was a significant difference in percent change from baseline in S-PMA between groups at Visit 5, with a greater increase from baseline observed for the control group (p=0.033); however, there was no significant difference in percent change from baseline S-PMA at any other visit (including the end of study visit) between study groups. There was no significant difference in absolute change from baseline in S-PMA between groups at any post-baseline visit.

The percent change from baseline in mean COHb was significantly different (p-values ranging from 0.003 to 0.045) between groups at all post-baseline visits; decreases in COHb were observed at most post-baseline visits for the test group while increases in COHb were observed at all post-baseline visits for the control group. For absolute change in COHb, a significant between-group-difference from baseline was only detected at Visit 5 (p=0.012) and at the end of study visit (p=0.024).

There was a statistically significant difference in percent change from baseline in mean exhaled CO at Visit 5 (p=0.028), with a decrease from baseline mean CO observed for the test group and an increase from baseline mean CO in the control group. Although these changes in mean CO were also observed at other study visits (including the end of study visit), these changes were not significantly different between groups. Decreases from baseline in mean CO were also observed in the test group at all post-baseline study visits in analyses of absolute change from baseline; however, there were no significant differences in exhaled CO between study groups at any post-baseline visit.

The applicant's literature review included information on BOE comparisons between cigarette use and oral nicotine product use. One study found that, of smokers who switched to oral nicotine products, total NNAL and exhaled CO were significantly reduced compared to baseline UB cigarette smoking in smokers (n=49) who switched to Exalt smokeless tobacco, Ariva dissolvables, or NRT lozenges for 2 weeks (45). NNAL was significantly higher in smokers who switched to Exalt compared to using NRT gum. There were no significant differences in NNAL between Ariva and NRT gum users. Blank and Eissenberg (44) conducted a study where cigarette smokers (n=21) completed four 5-day conditions of either smoking UB cigarettes, using Ariva dissolvables, using Camel Snus (various flavors), or abstaining from all tobacco. Exhaled CO was significantly reduced in smokers who used Ariva and Camel Snus compared to smoking UB cigarettes. Exhaled CO levels in Ariva and Camel Snus were comparable to the tobacco-abstinent group. However, there were no significant differences in total NNAL levels for the dissolvable or the tobacco-abstinent groups compared to UB cigarette smoking across the five-day study period.

Overall, these studies summarized by the applicant suggest that TNE and some non-nicotine BOE are significantly reduced in cigarette smokers who switch completely to oral tobacco products. However, the majority of individuals who use oral tobacco products are dual tobacco users, and very few smokers switch completely. Therefore, most smokers who use oral tobacco products will likely dual-use the products with their UB cigarettes. Smokers interested in using oral nicotine products to significantly reduce (i.e., 60% or greater), but not quit, smoking may experience reductions in BOE, primarily CO, COHb, and TNE, depending on the extent to which smoking is reduced. One study suggests that a 60% reduction in CPD translates to significant reductions in TNE and multiple non-nicotine BOE. However, in general, smokers who dual-use cigarettes and non-NRT oral tobacco products may not experience reductions in BOE compared to smoking UB cigarettes, particularly if they do not substantially reduce their CPD upon initiating use of oral tobacco products.

2.4.5.2 Dual Use and Non-compliance

Dual use with oral tobacco products, as shown by both the applicant's studies and the literature review summarized in the PMTAs, is common. The one study that the applicant conducted to measure BOE did not include a group that exclusively used the test product (a prior version of VERVE® Discs Blue Mint (Gen 2; VBM-FG2)) but had two groups of smokers, one that also had ad libitum access to the test product and the other that did not. In other words, both groups continued to smoke. The lack of a difference in NNAL levels is confounded by the smoking. It is likely that a VERVE® product-only group would show a decrease in NNAL, given the significantly lower levels of NNK in the VERVE® products, as compared to cigarette smoke yields. This is true of comparison to smokeless tobacco as well.

2.4.5.3 Summary of BOE Findings

The applicant submitted one study that measured BOE in users and this was conducted with a prior version of VERVE® Discs Blue Mint (Gen 2; VBM-FG2), not the products that are the subject of the PMTAs. There was no test product-only group; therefore, no information on what might be expected if a

smoker were to switch to VERVE® products (or one similar to the PMTA products) is available. However, the data that were submitted do not show an increase in BOE in the group that continued to smoke and had ad libitum access to the test product compared to smoking alone. That is, using VERVE® products in addition to smoking cigarettes, even if CPD does not change, does not result in higher BOEs. In addition, the literature suggests that smokers who switch to from cigarettes to oral nicotine tobacco products will have reductions in BOE, including nicotine, CO, and COHb.

As noted in Section 2.2 of this review, the chemistry review identified a potential deficiency in the bioanalytical testing information used in the biomarkers of exposure (BOE) study. However, the BCP review described adequate reference HPHC data and other scientific evidence to provide confidence in the BOE and use behavior for the VERVE® PMTA products.

2.4.6 Adverse Health Effects

The medical review primarily focused on the analysis of AEs associated with the five clinical studies as well as AEs reported to the ALCS Consumers Call Center, which included AEs on products similar to VERVE®. In addition, the medical review evaluated AEs reported in the literature for oral nicotine products similar to VERVE®. The medical reviewer noted that none of these studies evaluated biomarkers of potential harm or were designed to evaluate health effects. The studies include one study assessing associated BOE of a prior version of VERVE® Discs Blue Mint (VBM-FG2), one PK study of VERVE® Discs Blue Mint prototype products, and three abuse liability studies including either VERVE® Discs or Chews. Additionally, the medical review analyzed three different categories of scientific literature submitted by the applicant: a review of the scientific literature on health effects associated with nicotine and other ingredients in the new products; "authoritative statements" released by public health agencies on nicotine-associated health effects organized by selected diseases (e.g., cardiovascular disease, diabetes); and a compilation of diverse interventional and observational studies and case reports on nicotine-related health effects.

The five studies evaluated in the medical review are as follows:

- **Study COV-VER-01-13 / Covance Study No. 8290036**
  A Randomized, Controlled, Parallel Group Pilot Clinical Study to Determine Changes in Biomarkers of Exposure (BOE) in Adult Smokers Allowed Ad Libitum VBM-FG2 Disc Use Relative to Adult Smokers Not Allowed VBM-FG2 Disc Use
- **Study ALCS-RA-16-19-VRV / CA201617**
  Characterization of Nicotine Exposure Profiles and Subjective Measures of VERVE® Discs Products for Abuse Liability Determination in Adult Smokers Relative to Combustible Cigarettes and Nicotine Gum (this was repeated due to expired Nicorette gum used in the original study)
- **Study ALCS-RA-16-23-VRV / CA20655**
  Characterization of Nicotine Exposure Profiles and Subjective Measures of Products Currently Marketed As VERVE® Chews for Abuse Liability Determination in Adult Smokers Relative to Combustible Cigarettes and Nicotine Gum
- **Study ALCS-RA-16-26-VRV / CA21469**
  Characterization of Nicotine Exposure Profiles and Subjective Measures of VERVE® Discs Products for Abuse Liability Determination in Adult Smokers Relative to Combustible Cigarettes and Nicotine Gum (this is the repeated study of ALCS-RA-16-19-VRV)
- **Study** (b) (4)
  (b) (4)

Overall, there were no reports of either serious AEs or deaths in any of the five clinical studies. The combined total of subjects from each of the studies was 253 participants. Of these, 79 participants reported a total of 144 AEs. A majority (70.3%) of AEs were assessed by the principal investigators to be not related or unlikely related to the use of VERVE® products. AEs assessed as likely or possibly related to the use of VERVE® products comprised 29.7% of all reported AEs.

Additionally, all AEs were assessed by the principal investigators for severity (i.e., mild, moderate, severe or serious). Of these, 94.5% of AEs reported among study participants using VERVE® products were considered mild and 5.5% were assessed as moderate. All 27 AEs deemed likely or possibly related to the use of VERVE® products were considered mild. There were no severe or serious AEs reported.

Respiratory, thoracic and mediastinal disorders comprised 34.1% of all AEs reported in the VERVE® clinical studies and were the most prevalent system organ class (SOC) for AEs assessed likely or possibly related to VERVE® products, followed by gastrointestinal (GI) disorders, nervous system disorders and nutrition and metabolism disorders.

The top Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms identified for AEs likely or possibly related to VERVE® products were headache, cough, throat irritation, nasal congestion, oropharyngeal pain, dyspepsia and dizziness.

The medical review of the data from the ALCS Consumer Call Center AE data repository noted that the information included data collected between May 2012 and December 2017. Four AEs were reported to the ALCS Consumer Call Center. Three of the four consumers each reported one AE associated with the use of VERVE® Blue Mint Discs and one consumer reported an AE associated with VERVE® Harvest Blend discs. Although all four AEs were “mild in severity” and “unexpected,” the three AEs reported in association with Blue Mint Discs included one incident of choking (2012) and two incidents of tooth fracture (2013). Detailed background information on these AEs was not provided. The tooth fractures would have been with a prior version of the current VERVE® product similar to VERVE® Discs Blue Mint. The applicant notes a change in 2013 to the marketed prior version of the current VERVE® Discs Blue Mint that included a change in the “product texture”.

In addition to the limited AE information from the applicant’s own data, the PMTAs also included a summary of authoritative statements from public health agencies regarding generic nicotine health effects by topic area including cardiovascular, reproductive and developmental, GI, diabetes and carcinogenicity effects. Multiple references (many of which were foundational in the genesis of these widely accepted public health statements) on generic nicotine health effects are also cited in this application.

The applicant’s literature review provides the scientific framework for understanding nicotine-associated health effects; the medical reviewer noted that it does not address potential health risks linked to VERVE® products. Only two of the numerous studies provided by the applicant were product-specific (37, 46). However, these studies were not designed to assess health effects and neither of the publications reported AEs.

The applicant acknowledges the paucity of data on health risks associated with VERVE® products and with oral NRT as a major limitation in predicting health effects specific to VERVE® products. While the applicant acknowledges limitations and the applicant does not bridge existing data to VERVE® products, no serious and unexpected AEs were reported. Additionally, the applicant submitted a compilation of interventional and observational studies and case reports on generic nicotine-associated health effects.

2.4.6.1. Health Risks to Non-Users

The applicant stated that packaging for the VERVE® Chews and Discs products is child-resistant and compliant with Consumer Product Safety Commission 16 CFR 1700.15(b)(1). There was no discussion or specific information regarding accidental exposures or secondary exposures. Use of VERVE® Chews and Discs products is not associated with significant second-hand exposure which, in this respect, decreases risk for both users and nonusers.

2.4.6.2. Consumer Use and Potential Misuse

The applicant did not submit any information on consumer use and potential misuse for evaluation in the medical review. However, the BCP review addressed potential misuse through the evaluation of the applicant's actual use studies of VERVE® Discs and Chews. These data indicate that the majority of consumers use one disc or chew at a time, but approximately 30-43% use two or more discs or chews simultaneously. Based on the plasma nicotine concentrations associated with VERVE® Discs and Chews compared to cigarette smoking, it is unlikely that consumers who use 2-3 VERVE® Discs and Chews simultaneously would be exposed to higher levels of nicotine or other BOE compared to cigarette smoking. Thirty-eight percent reported using a VERVE® product while smoking a cigarette. There were no specific data provided to determine how use of multiple VERVE® products during a single use session or smoking while using VERVE® products may affect BOE. However, based on the plasma nicotine concentrations associated with VERVE® Discs and Chews compared to cigarette smoking, it is unlikely that consumers who use 2-3 VERVE® Discs and Chews simultaneously would be exposed to higher levels of nicotine or other BOE compared to cigarette smoking. FDA has also determined that there are no relevant concerns with using NRT gum concurrent with smoking, which has a higher nicotine C_{max} than VERVE® Discs and VERVE® Chews. (52). Therefore, it is unlikely that consumers would be exposed to greater levels of nicotine or other tobacco-related BOE following misuse of VERVE® Discs and Chews (based on the incidences of misuse reported in the applicant's actual use studies).

2.4.6.3. Health Risks Associated with Poly-use

The applicant did not submit any information on the health risks associated with polytobacco use and VERVE® for evaluation in the medical review. However, the BCP review addressed the poly-use issue. The applicant's in-market survey, actual use survey, BOE study, and literature review indicate that most tobacco users who use VERVE® dual or poly use with cigarettes. In particular, the applicant-submitted in-market survey, which gives an indication of real-world VERVE® use, found that all current users of VERVE® products also used one or more other tobacco products. Some smokers may replace one of their non-cigarette tobacco products with VERVE®, although a small portion (22%) may progress to polytobacco use with VERVE® products. Approximately half of smokers (51%) who used multiple tobacco products, including VERVE®, generally decreased their CPD while using VERVE®, while the other half of smokers either maintained (38%) or increased (11%) their CPD. For other tobacco product use, the majority of smokers reported either maintaining (47%) or increasing (15%) their non-cigarette tobacco use when starting VERVE®. As VERVE® and oral tobacco products are actually used (i.e., dual or poly-use while maintaining or modestly reducing CPD or other tobacco use), consumers are unlikely to experience significant reductions in BOE compared to exclusive UB cigarette smoking. However, if consumers were interested in using VERVE® to reduce CPD, studies suggest that a 60% reduction in CPD while using oral tobacco products may lead to significant reductions in many BOE compared to exclusive UB cigarette smoking. Even a modest reduction (< 50%) in daily cigarette consumption may reduce the risk of tobacco related disease due to a decreased exposure to HPHCs.

2.4.6.4. Health Risks Associated with Switching to these Products Compared to Continued Smoking

The BCP review addressed the likelihood of and health effects associated with switching to use of VERVE® products from cigarettes smoking. The applicant-submitted literature review indicates that smokers who switch completely to oral nicotine tobacco products reduce exposure to several BOE associated with cigarette smoking, including TNE, CO, and COHb. The applicant-submitted 6-week actual use study indicates that a subset of smokers report switching completely to VERVE® products (11%). Controlled trials (identified from the applicant-submitted literature review) found that smokers who switched completely to oral nicotine tobacco products or who immediately reduced CPD by 60% or more upon initiating use of oral nicotine tobacco products significantly reduced exposure to TNE, CO, COHb, and other non-nicotine BOE. However, smokers who reduced CPD gradually over 3 weeks did not significantly differ in BOE from UB cigarette smokers. Given the bridging information for VERVE® and other oral dissolvable tobacco products (provided by the chemistry reviewer; see Appendix Tables 16 and 17), if smokers gradually reduce and ultimately maintain a 60% reduction in CPD while using VERVE®, it is likely that nicotine and many other non-nicotine BOE would be reduced. Among smokers who switch completely to oral tobacco products, CO levels are comparable to being tobacco abstinent (i.e., comparable to smokers who abstained from all tobacco use for 5 days). However, given that these outcomes in the actual use studies and the literature review were based on short-term assessments (e.g., one week of use) and products were often provided free of charge, the generalizability of these findings to real-world use is limited. The applicant's in-market evaluations of VERVE®, which provided real-world assessment of VERVE® products on the market, found that 13% of smokers replaced their non-cigarette tobacco use with VERVE® (but continued smoking) and 2% of smokers switched from cigarettes to VERVE® (but continued using other non-cigarette tobacco products). No current VERVE® consumers switched completely from all tobacco products to exclusive VERVE® use. Furthermore, the applicant's abuse liability studies indicated that abuse liability and acceptability of VERVE® products is lower than for UB cigarettes and comparable to NRT gum. The 12-week actual use studies indicated that VERVE® acceptability among smokers declines over time. Therefore, only a small percentage of smokers are likely to switch to exclusive VERVE® product use.

2.4.6.5. Health Risks Associated with Switching to this Product Compared to Tobacco Cessation

The applicant did not provide information comparing the short- and long-term health effects of complete or incomplete VERVE® switching to abstinence. However, the BCP review addressed the health effects associated with switching to use of VERVE® products from cigarettes smoking compared to tobacco cessation. The applicant's in-market survey and literature review indicate a low likelihood of former smokers relapsing to tobacco use with VERVE® or oral tobacco products. The in-market survey evaluated the percentage of VERVE® product ever triers who had been former tobacco users and then relapsed to using the tobacco product they had quit. No VERVE® product ever triers reported re-initiating cigarette smoking after first trying a VERVE® product. Two percent of VERVE® product ever triers reported re-initiating to another tobacco product (other than cigarettes and VERVE®) after first trying a VERVE® product.

The in-market survey also indicates that 4-5% of VERVE® ever triers quit using all tobacco products after trying VERVE® products; however, it cannot be determined whether VERVE® was the catalyst for tobacco product cessation. A study in the literature review indicates that 20-25% of smokers interested in quitting smoking maintain use of oral tobacco products instead of quitting cigarettes; however, participants were instructed on how to use the oral tobacco products to assist with quitting smoking and it is unclear whether consumers would normally initiate these non-NRT products with the intent of

quitting smoking. Given that the consumer population most likely to initiate VERVE® use is current smokers who also use one or more other tobacco products and that VERVE® products will not be marketed as cessation products, it is unlikely that smokers who are interested or motivated to quit smoking would initiate VERVE® for this purpose. However, based on the BOE data provided and bridging data on HPHCs present in VERVE® Discs and Chews compared to other tobacco products (Appendix Tables 16 and 17), if consumers quit smoking or substantially reduce their CPD (i.e., by 60% or greater) but continue use of VERVE® products, exposure to many HPHCs, including nicotine, CO, COHb, and other non-nicotine BOE, would be significantly reduced compared to smoking cigarettes.

2.4.6.6. Health Risks Associated with Switching to Product Compared to Cessation Medication

The applicant did not provide clinical data to evaluate the relative health risks of switching to VERVE® products compared to cessation medication. However, as the BCP review noted, based on the BOE data provided and bridging data on HPHCs present in VERVE® Discs and Chews compared to other tobacco products (Appendix Tables 16 and 17), if consumers quit smoking or substantially reduce their CPD (i.e., by 60% or greater) but continue use of VERVE® products, exposure to many HPHCs, including nicotine, CO, COHb, and other non-nicotine BOE, would be reduced compared to smoking cigarettes.

2.4.6.7. Summary of Adverse Health Effects

The applicant submitted a dearth of health effects data specific to VERVE® products. The five short-term clinical studies that were submitted with this application did not include clinical endpoints or BOPH. No serious AEs were reported, and the majority of reported AEs were mild in severity. Additionally, data from the ALCS Consumer Call Center were quite limited and did not inform an assessment of health effects. In lieu of providing product-specific substantive evidence regarding the health impact of VERVE® products, the applicant conducted an integrated nonclinical and clinical risk assessment. The applicant stated that its approach assumes that "any health risks would be related to the individual ingredients…" Health effects associated with individual ingredients are addressed in Section 2.3 of this review.

The applicant has demonstrated that, if smokers were to switch to the VERVE® Discs and Chews (i.e., quitting cigarettes), there would likely be health benefits. There would likely also be health benefits if smokers reduced their cigarette use due to use of the VERVE® products. As the review of the PMTAs shows, dual or poly use is common with oral tobacco products, including the VERVE® products. The HPHC information also indicates the potential for health benefits if a polytobacco user were to replace a smokeless tobacco product with a VERVE® product.

2.4.7. Likelihood of Product Misuse or Malfunction

The applicant did not submit information on potential misuse or malfunction of the VERVE® products. However, as noted in section 2.4.6.2 of this review, it is unlikely that a user of VERVE® products would be exposed to greater nicotine or other tobacco-related BOE following misuse of VERVE® Discs and Chews. This is based on the applicant's actual use studies.

2.4.8. Bioresearch Monitoring (BIMO) Inspection

OS reviewers did not identify any substantive concerns pertaining to the submitted clinical studies and did not recommend BIMO inspection. FDA's Office of Compliance (OCE) review of the submission did not reveal any data integrity or human subject protection concerns and agreed with OS reviewers that BIMO inspections for the protocols submitted and associated sites were not warranted.

2.4.9. Summary of Individual Health Findings

The BCP review concluded that VERVE® Discs and Chews in Blue Mint and Green Mint flavors are associated with lower plasma nicotine concentrations and lower positive subjective ratings compared to UB cigarettes, reducing their abuse liability and likelihood of use for youth, non-smokers, and former smokers. The abuse liability of VERVE® products was similar to that of nicotine gum.

Current smokers who also use one or more other tobacco products are the consumer population most likely to try VERVE® products. The data and literature review submitted by the applicant suggest that smokers who completely switch to VERVE® products or reduce their CPD by 60% or more upon initiating oral tobacco products may reduce their exposure to nicotine and other non-nicotine BOE. However, low subjective appeal and increased craving and withdrawal may prevent current smokers from fully transitioning to VERVE® products. Data from the applicant's submitted studies suggest that few smokers (11%) switch completely to VERVE® or oral tobacco products, but these data are based on one week of use and do not reflect the measured decline in VERVE® acceptability among smokers that was captured in the applicant's 12-week actual use study. Therefore, the percentage of complete switching would likely be lower than the identified percentage in the applicant's study. Dual or poly use is the primary use behavior expected of VERVE® product users. Smokers who dual use VERVE® products with cigarettes and do not substantially reduce their CPD (i.e., by 60% or greater) do not reduce their exposure to nicotine or non-nicotine BOE.

As TPL, I agree with the BCP review conclusions that if smokers switch to VERVE® or significantly reduce CPD, they would see a reduction in BOE. Certainly, the likelihood of a larger number of smokers making such changes is low, given the low appeal of the product and the polytobacco use with oral tobacco products. However, data support the potential for a small percentage of smokers to make such changes. Additionally, the reduced abuse liability and likelihood of use by youth, as well as non- and former-smokers, is small for the VERVE® products if marketed.

The medical review concluded the following:

- There was a dearth of health effects data associated with VERVE® products in this application. Although five short-term clinical studies were submitted relating to VERVE® products, prior versions, or prototypes, they were not designed to collect individual health data. Moreover, none of the studies included clinical endpoints or BOPH data.
- The AE findings for each of the five clinical studies did not provide additional clinical insight on potential health risks related to VERVE® products. Consequently, these data were neither substantive nor helpful in addressing short-term or long-term health effects associated with the new products.
- The AE data culled from the ALCS Consumer Call Center represented events that occurred in 2012 and 2013 and may be linked to earlier versions of VERVE® Discs Blue Mint. Since the applicant did not cite potential differences between the prior versions of VERVE® Discs Blue Mint and the current VERVE® product, the applicability of these AE reports is unclear.
- Data compiled from the published literature on AEs associated with similar products do not provide substantive clinical evidence to identify potential health risks associated with VERVE® products.
- Although multiple authoritative statements on the effects of nicotine on organ systems were referenced by the applicant, specific bridging of these findings to the VERVE® products is absent from this application.
- The applicant does not bridge findings from generic nicotine studies to the use of nicotine in the context of VERVE® products.

- The applicant attempts to extrapolate data from NRT studies to the new products; however, the applicant did not present studies to corroborate these inferences.

The medical review concluded that there are limitations in demonstrating the potential health impact of the new products on users and that the applicant did not bridge data from the published literature and early VERVE® prototypes and prior versions of VERVE® Discs Blue Mint to the PMTA VERVE® products. Overall, the medical review concluded that, from the medical perspective, the information presented in the application has two limitations, described below.

First, although the applicant acknowledges the evolution of VERVE® products from earlier generations, the applicant does not explain the similarities and differences between each of the earlier prototypes and the current new products or the potential effects on user behavior, exposure and health risks. Additionally, detailed information regarding composition and formulation changes during each generation was not submitted. From the medical perspective, we are unable to bridge information from the prototypes to the new products in the clinical studies, which limits the medical assessment. Additional information is necessary for FDA assess the prototype differences with respect to user behavior, exposure and health risks - specifically: identifying information (i.e., name(s) of the prototype and reference number(s); years when the prototype was initially created, marketed, and removed from the market (if applicable); and title and year of all industry and non-industry sponsored research studies associated with each prototype.

Second, the applicant's assessment of health risks is based on a clinical assessment of nicotine and a non-clinical assessment for other ingredients. Although the applicant references multiple studies on generic nicotine- and NRT-associated health effects, these findings are not bridged to the new products. FDA needs detailed information from the scientific literature to assess potential differences in user exposure and the health effects of these new products. Bridging information to justify extrapolating findings from generic nicotine and NRT studies to substantiate health effects for the current new tobacco products is necessary to adequately assess the applicant's health risk assessment.

As TPL, I agree with the medical review in that insufficient clinical study data was submitted with this PMTA. Clinical studies designed to delineate the health effects of new products, alone and in combination with other tobacco products if there is evidence that the new products would be used in conjunction with other tobacco products, can provide evidence of short-term, and possibly long-term, health effects. However, the chemical composition of the new products, along with adequate toxicology information on ingredients, provide sufficient information to support an overall determination that the marketing of new products, from the standpoint of potential adverse health effects, are appropriate for the protection of the public health. In addition, the limited information available on AEs, though not designed to evaluate health effects, does not raise concerns about issuing marketing orders. There is also information from the ALCS Consumers Call Center when the first- and second-generation (Gen 1 and 2) VERVE® Discs Blue Mint products, and then later the current four new products, were on the market in Virginia. These sources of information do not indicate any SAEs.

2.5. Population Health

Several studies in the PMTAs provided information regarding the likelihood of use of the VERVE® products. These include: (1) 6-week actual use study of oral tobacco-derived nicotine products currently marketed as VERVE® Discs and VERVE® Chews, (2) VERVE® Discs 12-Week Extended Home Use Test Final Report Final—PowerPoint Presentation, and (3) ALCS In-Market Adult Consumer Study (MACS): Oral Tobacco-Derived Nicotine Products Currently Marketed as VERVE® Products. These studies were evaluated in both the epidemiology and BCP reviews.

2.5.1. Likelihood of Use by Current Cigarette Smokers

The epidemiology review evaluated the applicant's 6-week actual use study in which the applicant presented evidence that smokers can adopt the use of VERVE® products within study conditions. The review also evaluated the results of an in-market cross-sectional VERVE® use survey (MACS) to support this finding. Studies indicate that 2-17% of current cigarette smokers can switch completely to VERVE® under actual use study conditions and free product availability, and a modest proportion of other tobacco product users and cigarette smokers (11%) can completely switch to VERVE®. However, most current tobacco users co-use VERVE® and cigarettes or other tobacco products (77-84%). MACS data indicated that 2% of current VERVE® users who reported daily or non-daily use in the past 30 days completely switched from cigarette smoking (retrospective exposure assessment). Because of free product availability and retrospective self-report, the actual use study results likely represent an upper-bound estimate of product use, and the results of the MACS are likely a more reasonable estimate. Taken together, research submitted by the applicant demonstrates that there is limited evidence that current cigarette smokers, including those intending to quit, would switch completely to the new tobacco products as currently used by consumers.

The BCP review also evaluated the likelihood of use by current tobacco product users. The BCP review noted that the applicant states that VERVE® products are designed to appeal to adult tobacco consumers, particularly adult cigarette consumers, who are interested in an alternative to their current tobacco product. The literature review and applicant-submitted studies support that current smokers are the population most likely to try oral tobacco products, including dissolvable tobacco and VERVE® products, often due to curiosity. Smokers interested in reducing cigarette smoking may also be motivated to start using oral tobacco products. However, the applicant's submitted abuse liability studies indicate that VERVE® Discs and Chews do not deliver nicotine as well as cigarettes and are not liked as much as UB cigarettes. The applicant's 12-week actual use study for a prior version of VERVE® Discs Blue Mint (Gen 1) also noted that product acceptability among smokers declined from Week 4 to Week 12 during the study. Therefore, VERVE® products are unlikely to be a suitable substitute for cigarettes, which reduces the likelihood of continued use for most smokers.

Current smokers who also use one or more other tobacco products are the consumer population most likely to try VERVE® products. The data and literature review submitted by the applicant suggest that smokers who completely switch to VERVE® products or reduce their CPD by 60% or more upon initiating oral tobacco products may significantly reduce their exposure to nicotine and other non-nicotine BOE. However, low subjective appeal and increased craving and withdrawal may prevent current smokers from fully transitioning to VERVE® products. Data from the applicant's 6-week actual use study suggest that few smokers (11%) switch completely to VERVE® or other oral tobacco products, but these data are based on a single week (Week 6) in the 6-week study and do not reflect the measured decline in VERVE® acceptability among smokers that was captured in the applicant's 12-week actual use study for a prior version of VERVE® Discs Blue Mint (Gen 1). Therefore, the percentage of complete switching would likely be lower than the identified percentage in the applicant's study. Dual or poly use is the primary use behavior expected of VERVE® product users.

The BCP review noted that the in-market survey also indicates that 4-5% of VERVE® ever triers quit using all tobacco products after trying VERVE® products; however, it cannot be determined whether VERVE® was the catalyst for tobacco product cessation. A study in the literature review indicates that 20-25% of smokers interested in quitting smoking maintain use of oral tobacco products instead of quitting cigarettes; however, participants were instructed on how to use the oral tobacco products to assist with quitting smoking and it is unclear whether consumers would normally initiate these non-NRT products

with the intent of quitting smoking. Given that the consumer population most likely to initiate VERVE® use is current smokers who also use one or more other tobacco products and that VERVE® products will not be marketed as cessation products, it is unlikely that smokers who are interested or motivated to quit smoking would initiate VERVE® for this purpose. However, based on the BOE data provided and bridging data on HPHCs present in VERVE® Discs and Chews compared to other tobacco products (Appendix Tables 16 and 17), if consumers quit smoking but continue use of VERVE® products, exposure to many HPHCs, including nicotine, CO, COHb, and other non-nicotine BOE, would be reduced compared to smoking cigarettes.

2.5.2. Summary of Likelihood of Use by Current Cigarette Smokers

As TPL, I agree with the epidemiology and BCP reviews and the conclusion that there is limited evidence that current smokers would switch completely to the VERVE® products. While 2-17% of smokers did switch completely to VERVE® in the applicant's studies, the actual use studies have limitations and 17% is likely an upper-bound estimate; the in-market VERVE® use survey, which noted 2% of current VERVE® users switched from cigarette use, is likely more accurate. However, results do not suggest that smokers are likely to increase their overall tobacco product use when initiating VERVE® Discs or Chews; BOE were not increased in study participants allowed cigarettes ad libitum.

2.5.3. Poly Use of VERVE® and Cigarettes or Other Tobacco Products

The epidemiology review noted that 52% (n=270) of the applicant's actual use study participants, upon enrollment, reported also using other tobacco products in the past 30 days. Therefore, poly use was common among participants (all were past 30-day smokers, and over half were also other tobacco product users). Based on the MACS and the 6-week actual use study, the applicant confirmed that most VERVE® users are dual or poly users of VERVE® products with other products; however, the applicant also notes that a reduction in cigarette consumption accompanies co-use of tobacco products. At the end of the 6-week actual use study, all participants (100%) reported "starting to use" a VERVE® product, which was defined as using 20 or more VERVE® Discs or Chews during the 6-week study. The proportion of participants that reported using VERVE® products only during the study increased from 7.35 % in Week 1 to 17.41% in Week 6, while the prevalence of dual or poly use of VERVE® with other tobacco products including cigarettes decreased.

The epidemiology review noted that observational studies submitted in support of this application demonstrate that dual use of VERVE® with cigarettes is common among adult VERVE® product users. In the 6-week actual use study, among participants who completed the 6-week study and the end of study (EOS) survey, 17.4% reported using VERVE® only (complete switchers), 1.4% reported only cigarette smoking, 64.4% reported dual using VERVE® and cigarettes, 5.8% reported using VERVE® and other oral tobacco products, and 10.4% reported using VERVE® and other tobacco products and cigarettes. Among those who completed the study and who reported past 30-day use of other tobacco products at screening (137 of total n= 517), 20.4% reported dual use of VERVE® and other tobacco products at the EOS. The applicant noted that the proportion of participants who reported dual using at screening decreased over time in the actual use study. The applicant stated that although dual use with cigarettes is the predominant VERVE® tobacco user pattern, dual users report a reduction in CPD. In the actual use study, 58% of the total study sample (2-day pilot test and 6-week actual use test) reduced their screening-level daily cigarette consumption by 20% or more on days smoked, and of this group 77% were dual users. Screening to Week 1 CPD consumption decreased by 5 CPD (13 to 8 CPD), while Week 1 to Week 6 CPD reduction was 2 CPD (8 CPD to 6 CPD). In the MACS, the applicant stated that 48 of 52 (92.3%) current VERVE® product users were dual users with cigarettes, and 50% of these users reported using fewer cigarettes when using VERVE® than before starting to use VERVE®. The applicant further

claimed that the amount of VERVE® use is related to the number of CPD in both the actual use study and the MACS. In the actual use study, regression analyses suggested a statistically significant decrease in CPD consumed by number of VERVE® products consumed (beta=-0.15 (95% Cl -0.17, -0.14)). Overall, given the totality of tobacco use behavior data submitted by the applicant, it appears highly likely that most VERVE® product users would also use other tobacco products including cigarettes, and among dual users the reduction in smoking is modest (2-3 CPD). Epidemiological studies indicate that the health benefit of smoking reduction (CPD) by less than 50% is unclear. However, some participants were able to reduce CPD by 50% or more (n=8).

The BCP review noted that in the 6-week actual use study, the percentage of participants who reported using only VERVE® and no other tobacco products increased from 7% to 17% across the 6-week study. The percentage of participants who reported using VERVE®, cigarettes, and other tobacco products (i.e., polytobacco users) declined from 20% to 10% during the study. Alternatively, the percentage of dual users (VERVE® and cigarettes or VERVE® and other tobacco products) did not substantially change over the 6-week use period. Overall, the percentage of participants who reported using VERVE® with any tobacco product (cigarettes and one or more other tobacco products) declined from 93% (Week 1) to 81% (Week 6). The findings in this study, according to the BCP review, suggest that the majority of smokers who initiate use of VERVE® products may become dual users of cigarettes and VERVE®. Smokers who dual use cigarettes and VERVE® decrease their CPD by a net 20% from prior to using VERVE®. Of smokers who also currently use other tobacco products, the majority may replace their non-cigarette tobacco product use with VERVE®. Twenty-two percent of participants may become poly users of cigarettes, other tobacco products, and VERVE®. However, the decreases in prevalence of cigarette smoking and other tobacco product use across 6 weeks when initiating use of VERVE® suggest that some smokers may titrate their product use to maintain sufficient levels of nicotine. Results do not suggest that smokers increase their overall tobacco product use when initiating VERVE® Discs or Chews.

The BCP review concluded that the MACS, actual use survey, BOE study, and literature review indicate that most tobacco users who use VERVE® dual or poly use with cigarettes. In particular, the applicant-submitted in-market survey, which gives an indication of real-world VERVE® use, found that all current users of VERVE® products also used one or more other tobacco products. Some smokers may replace one of their non-cigarette tobacco products with VERVE®, although a portion (22%) may progress to polytobacco use with VERVE® products. Approximately half of smokers (51%) who used multiple tobacco products, including VERVE®, generally decreased their CPD while using VERVE®, while the other half either maintained (38%) or increased (11%) their CPD. For other tobacco product use, the majority of smokers reported either maintaining (47%) or increasing (15%) their non-cigarette tobacco use when starting VERVE®. As VERVE® and oral tobacco products are actually used (i.e., dual or poly use while maintaining or modestly reducing CPD or other tobacco use), consumers are unlikely to experience significant reductions in BOE compared to exclusive UB cigarette smoking. However, if consumers were interested in using VERVE® to reduce CPD, studies suggest that a 60% reduction in CPD while using oral tobacco products may lead to significant reductions in many BOE compared to exclusive UB cigarette smoking.

2.5.4. Summary of Poly Use

As TPL, I agree with the epidemiology and BCP reviews that there is evidence that smokers who use VERVE® are likely to use other tobacco products including cigarettes; however, their total combusted tobacco product consumption and toxicant exposure are not likely to increase and may be lower for the small percentage of poly users who reduce overall CPDs compared to smokers who do not reduce overall CPD. Further, the results of the clinical AUS suggests a substantial proportion of non-cigarette tobacco users (46-68%) successfully switch to the new tobacco product. HPHC information submitted by

the applicant indicates the potential for health benefits if a polytobacco user were to replace a smokeless tobacco product with a VERVE® product.

2.5.5 Use by Former or Never Smokers

The epidemiology review noted the applicant presented evidence using surrogate products to demonstrate that initiation of tobacco use with VERVE® products is unlikely. Prevalence of use of dissolvable tobacco products and NRT is low, and prevalence of dissolvables as the first tobacco product used is <1%. In the MACS, in which the applicant surveyed VERVE® product users in the test market (Virginia), there were no adult participants who reported first tobacco use with VERVE® products. Among adult users of VERVE® products, two MACS participants (1%) reported re-initiation of tobacco products using VERVE® after successful smoking cessation for six months or more, and both reported co-use of other tobacco products with VERVE®. Synthesizing data across diverse lines of evidence, the applicant concluded that the likelihood that adult nonusers will initiate tobacco product use with VERVE® is low. This conclusion is based upon results from the Perception and Behavioral Intention (PBI) study, which indicate a low intention to try and to use the product among adults, including young adults aged 18-24 years, and the observation that most VERVE® users in the MACS were current tobacco users when they first started to use VERVE® (there was little evidence of tobacco use initiation with VERVE® products from the cross-sectional survey). The applicant extrapolated results regarding youth initiation of tobacco use with dissolvable tobacco products and NRT from national surveys to potential youth use of VERVE® products and concluded that the prevalence of use of dissolvable tobacco products among youth would be low. Furthermore, the applicant stated that given that the likelihood of nonusers initiating tobacco use with VERVE® is low, the probability of transitioning to cigarettes is also low. The applicant cited results of its own secondary data analysis, which illustrates that use of dissolvable tobacco products is associated with lower probability of future cigarette smoking (PATH data). Overall, the applicant concluded that the effect of marketing VERVE® products on nonusers is likely to be small. Therefore, using both surrogate data and direct surveys, the applicant supports that the probability of initiation or re-initiation of tobacco use with VERVE® products is low.

There are no longitudinal data to assess the probability of nonuser initiation of tobacco use with VERVE® products. The applicant's MACS reported that among VERVE® current and past product users who enrolled in the survey, none reported that their first tobacco product ever tried or ever tried consistently was a VERVE® product. Results of the applicant's literature review support that less than 2% (1.2-1.6%) of adults report ever trying a dissolvable tobacco product. Furthermore, among college students, the applicant cited studies in which 4.5% of participants reported using an "emerging tobacco product" including a dissolvable, snus or e-cigarette as the first tobacco product ever tried, and most reported use of e-cigarettes. ln the same study of college students, less than 1% (0.1%) of participants reported initiation with a dissolvable tobacco product among current tobacco users. The applicant stated that in the PATH Wave 1 study data, the prevalence of current use of dissolvable tobacco products was 0.2% among young adults and 0.1% among adults. Results of the applicant's literature review support that 1.2-1.6% of current tobacco users initiate tobacco use with a dissolvable, NRT, or other oral tobacco product. Extending these results to the VERVE® products, the applicant concludes that the likelihood that adult nonusers will initiate tobacco product use with the new products is low. Regarding re-initiation of tobacco use with VERVE®, the MACS identified two VERVE® ever-triers (1%) who reported smoking cessation for 6 months or longer before first trying a VERVE® product, and there were no other tobacco product users who had quit for 6 months or longer prior to first trying VERVE®.

The BCP review also assessed the potential for use by former or never smokers and the potential to progress to cigarette use. According to the BCP review, initiation among non-users for dissolvable

tobacco products is low, and current smokers do not report that they first initiated using tobacco with VERVE® products. These findings are supported by the applicant's literature review, which discusses initiation of oral tobacco products (e.g., dissolvable tobacco products) and the applicant's actual use studies on VERVE® products. Therefore, it is not anticipated that non-users will initiate tobacco use with VERVE®, and for those who do, there is low likelihood that they will progress to regular use of VERVE®, cigarettes, or other tobacco products after trying VERVE®. There is also low likelihood that former smokers will relapse to smoking if they try VERVE®; however, a small subset (2%) of smokers who report quitting other forms of tobacco may try VERVE® and relapse to non-cigarette tobacco product use. Smokers who currently use one or more other tobacco products are the most likely tobacco users to initiate and continue use of VERVE® or dissolvable tobacco products. The applicant-submitted actual use studies suggest that among current smokers who ever tried VERVE® products, none reported that they initiated tobacco product use with VERVE® products and later switched to cigarettes or other tobacco products. Studies in the literature review and the applicant's clinical studies support that nicotine delivery and subjective ratings for VERVE® and dissolvable tobacco products are low compared to cigarettes, indicating that these products have lower abuse liability compared to cigarettes. Given the low prevalence of initiation with oral dissolvable tobacco products among never users and the low abuse liability of VERVE® and oral dissolvable tobacco products, it is not anticipated that never users would initiate tobacco use with VERVE® and progress to regular use of VERVE®, cigarettes, or other tobacco products.

Based on the applicant's clinical studies, the BCP review concluded that the VERVE® products are associated with lower plasma nicotine concentrations and lower positive subjective ratings compared to UB cigarettes, reducing their abuse liability and likelihood of use for non-smokers and former smokers.

2.5.6 Summary of Use by Former or Never Smokers

As TPL, I agree with the epidemiology review that across the actual use study, MACS, literature reviews, and original data analyses presented to describe VERVE® product use and tobacco use behavior, the applicant demonstrated that: a large proportion of current tobacco users can start using VERVE® under actual use study conditions and free product availability; a modest proportion of current smokers switch completely to VERVE® product use (2% in the MACS, 17% in the actual use study); and 11% completely switch from all other tobacco product use. I agree with the BCP review that it is not anticipated that non-users will initiate tobacco use with VERVE®, and for those who do, there is low likelihood that they will progress to regular use of VERVE®, cigarettes, or other tobacco products after trying VERVE®. Submitted data suggest that there is also low likelihood that former smokers will relapse to smoking if they try VERVE®; however, a small subset (2%) of smokers who report quitting other forms of tobacco may try VERVE® and relapse to non-cigarette tobacco product use.

2.5.7 Use by Vulnerable Populations

2.5.7.1. Youth

The BCP review evaluated the applicant-submitted literature review to determine the likelihood that individuals, particularly youth and young adults, who initiate with dissolvable tobacco products similar to VERVE® would progress to regular tobacco product use. This assessment includes the likelihood of progression to regular tobacco use among never smokers and the likelihood of increased, dual, and/or polytobacco use among current smokers who start using dissolvable tobacco products.

Among youth, data also suggest that initiation and use of dissolvable products is low. A study using 2012 National Youth Tobacco Survey (NYTS) data of 11,667 middle school and 12,899 high school students

found that ever use of dissolvables was 1.4% and 2.5% among middle and high school students, respectively (50). Ever and current use of dissolvables was highest among youth who currently used other tobacco products (50). We note that dissolvable use is no longer estimated separately in the NYTS; Since 2013, the definition of smokeless tobacco use has broadened to include chewing tobacco, snuff, dip, snus, or dissolvable products. The 2020 NYTS reports current use of smokeless tobacco among surveyed to be 3.1% for high school students and 1.2% for middle school students (54). Data from another study evaluated past and current use of tobacco products among university students in North Carolina and Virginia. Among 1,656 students who reported current or former tobacco use, none had tried dissolvables as their first product (52). Among 743 current cigarette smokers in the study, 0.1% reported dissolvables as the first tobacco product tried, compared to 65% who reported cigarettes as the first tobacco product ever tried (52). Overall, studies from the literature indicate that less than 1% of non-users (youth and adults) initiate tobacco use with dissolvable tobacco products. Current tobacco users are the most likely to try dissolvable products, and dual users are the most likely to continue use of dissolvable tobacco products.

The BCP review also noted that in the applicant's clinical studies, VERVE® Discs and Chews in Blue Mint and Green Mint flavors are associated with lower plasma nicotine concentrations and lower positive subjective ratings compared to UB cigarettes, reducing their abuse liability and likelihood of use for youth, non-smokers, and former smokers.

In addition, the epidemiology review noted that the applicant reported that awareness of dissolvable tobacco products among youth is very low and reported an 0.1% prevalence estimate of adolescents who have ever used dissolvable tobacco products. In PATH, among the only 10 youth participants who used a dissolvable tobacco product, they used no more than 10 occasions in their lifetime and most (>70%) did not report use in the last 30 days. In the 2012 National Youth Tobacco Survey (NYTS), 2% of middle and high school students reported ever use of dissolvable products, and 0.7% reported past 30-day use. In the Monitoring the Future (MTF) study, use among 12th graders was 1.4%. The applicant extrapolated results regarding youth initiation of tobacco use with dissolvable tobacco products and NRT from national surveys to potential youth use of VERVE® products and concluded the prevalence of use of dissolvable tobacco products among youth would be low.

2.5.8. Summary of Use by Vulnerable Populations

As TPL, I agree with the epidemiology and BCP reviews that note that the information extrapolating dissolvable tobacco products to VERVE® from the literature and from national survey data support that there is little likelihood of youth initiating tobacco use with VERVE®. Also, the applicant's clinical studies show that the VERVE® products have lower plasma nicotine levels and lower subjective ratings compared to the participants' UB cigarettes, showing reduced abuse liability for the VERVE® products and therefore reduced likelihood of use by youth.

2.5.9. Population Modeling

To investigate the impact of VERVE® on the population as a whole, taking into consideration users and non-users of tobacco products, the applicant submitted the ALCS Agent-Based Model (ALCS ABM). The model keeps track of tobacco product use prevalence and all-cause mortality in a hypothetical population exposed to two tobacco product use behavior scenarios:

- **Base Case Scenario**: The prevalent behavior is the use of cigarettes together with a combination of snus and dissolvable tobacco products. The combination of snus and

dissolvable tobacco products is labelled as Novel Smokeless Tobacco (NST) products in the applications.

- **Modified Case Scenario:** Similar behavior as in the base case scenario with the addition of VERVE® (i.e., incorporating the VERVE® products into the NST products).

The statistics review noted two main limitations with the model. The model uses the year 2014 to introduce the NST product in the Base Case scenario and year 2018 to introduce VERVE® in the Modified Case scenario; this appears to be related to the availability of empirical data to inform input parameters (initiation, cessation, relapse, and others). However, the transition probability of smokers switching to VERVE® was derived from the applicant's 6-week actual use study, which includes VERVE® only. Other transition probabilities related to the VERVE® products were obtained in combination with the NST products. Thus, comparing the results between the two scenarios may not be sufficient to isolate the impact of VERVE® on the population based on all-cause mortality. That is, because the modified case scenario includes VERVE® in combination with NST products, it might not be possible to isolate the absolute impact of VERVE® on the U.S. population. Note also that because of the nature of the study design of the actual use study, the results of that study are not representative of the U.S population. Though these limitations could limit generalizability of the outputs from the model to the U.S. population, the study informs our evaluation of actual use.

The statistics review also noted that the approach outlined in the PMTAs to estimate mortality rates has several limitations. The approach was driven by the data sources the applicant selected to derive mortality rates. Other data sources could have resulted in a more reliable approach to estimate mortality rates. For example, a data source traditionally used to estimate mortality rates for the development of population models in tobacco regulatory science is the CDC mortality-link file. The statistics review concluded that, due to model limitations, the evidence generated from this model cannot solely provide evidence on the impact of VERVE® on the U.S. population.

The epidemiology review evaluated the applicant's public health impact (PHI) model. The model estimated that the introduction of VERVE® into the U.S. tobacco marketplace would reduce smoking prevalence by 0.07%, resulting in 19,000 smoking-related deaths averted over the 60-year modeling period. Modelers utilized publicly available data sources and justifiable modeling assumptions to produce this estimate. However, the estimate of prevalence of use of VERVE® use among smokers is derived from the applicant's actual use study and is likely overestimated due to elements of the study design, i.e., recruitment of high proportion of smokers who were former oral tobacco product users. It is pertinent to note that any AUS study will be performed under experiment conditions that cannot perfectly represent real-world conditions. The applicant acknowledged that changing the prevalence of VERVE® use greatly influences model estimates. The model estimated that a 0.56% reduction in smoking prevalence due to switching completely to VERVE® results in 146,000 deaths prevented, as compared to 19,000 deaths prevented in the main analysis. Conversely, they stated a 300% increase in VERVE® initiation among non-tobacco users (never and former smokers) would need to take place to obviate the benefit of smokers switching to the product.

2.5.10. Summary of Population Modeling

The epidemiology review noted that the applicant's model estimates 19,000 smoking-related deaths averted over the 60-year period due to the introduction of VERVE® to the U.S. market. While the statistics review noted limitations to the model, the epidemiology review concluded that the modelers used reasonable assumptions in the model. The epidemiology review does assert that the model likely overestimates the deaths averted due to the limitations in the actual use study design. While the statistics review noted that the model cannot solely provide evidence of the public health impact of

VERVE® on the U.S. population, the model is not the sole evidence of public health benefit provided in the PMTAs.

As TPL, I agree with the epidemiology review that the model estimate is likely an overestimate based on the actual use study data; however, the model does not predict an increase in smoking-related deaths due to the introduction of VERVE® into the U.S. market. While I agree with the statistics review regarding the limitations of the model (i.e., it might not be possible to isolate the absolute impact of VERVE® on the U.S. population because the model scenario includes VERVE® in combination with NST products) , the epidemiology review noted that the assumptions used are justifiable. The model, therefore, can be viewed as one piece of evidence that the introduction of VERVE® has the potential to avert some smoking-related deaths, despite the number presented being an overestimate. Therefore, while the findings from the model are likely overestimates, the model used justified assumptions and predicts an overall reduction of smoking-related deaths with the introduction of VERVE® into the U.S. tobacco marketplace.

2.5.11. Summary of Population Health Findings

The epidemiology and BCP reviews concluded that, evaluating the totality of the evidence including information available in published literature, the PMTAs do not raise concerns about issuing marketing orders. The epidemiology review noted that the PMTAs included several observational studies, literature reviews and secondary data analyses to demonstrate the that introduction of VERVE® products into the U.S. would result in a public health benefit to the population as a whole. The applicant presented evidence that smokers can adopt the use of VERVE® products in study conditions and presented results of a 6-week actual use survey to support this finding. Studies indicate 2-17% of current cigarette smokers can switch completely to VERVE® under actual use study conditions and free product availability, and a modest proportion of other tobacco product users (11%) completely switch to VERVE®. However, most current tobacco users co-use VERVE® with cigarettes or other tobacco products (77-84%). For several reasons due to study design and methods, the results of the 6-week actual use study likely represent an upper-bound estimate of product use, and the results of the MACS are likely a more accurate estimate. For the small percentage of smokers who switch completely as reported in the MACS (2%), there is a clear health benefit.

Using surrogate products, the applicant presented evidence to demonstrate that initiation of tobacco use with VERVE® products is unlikely. Based on the applicant's submitted data, prevalence of use of dissolvable tobacco products and NRT is low, and prevalence of first tobacco product used is <1% for these products. In the cross-sectional MACS, there were no adult participants who reported first tobacco use with VERVE® products. Among adult users of VERVE® products, two MACS participants reported using VERVE® after successful tobacco cessation for 6 months or more, and of these two participants, both reported co-use of other tobacco products with VERVE®.

The applicant's PHI model suggests that the introduction of VERVE® into the U.S. tobacco marketplace would reduce smoking prevalence by 0.07%, resulting in 19,000 smoking-related deaths averted over the 60-year modeling period. Modelers utilized publicly available data sources and reasonable modeling assumptions to produce this estimate. Though the estimate of prevalence of use of VERVE® and transition probabilities between smoking and VERVE® use are likely overestimated, the model estimates are reasonable given the inherent uncertainty of predicting future tobacco use behaviors.

As TPL, I agree that the PMTAs contain sufficient information to evaluate the potential population health effects. While the studies of the VERVE® products are limited, the applicant also provided extrapolations from literature and survey information on NRT and dissolvable tobacco products to the VERVE® products. Based upon available data regarding tobacco use initiation among youth and young adults

with oral nicotine products, it is unlikely that VERVE® will lead to increased initiation of tobacco products, as most VERVE® users are already tobacco users and dissolvable tobacco products are unlikely to be a tobacco users first product.

The applicant's studies show that most VERVE® users are polytobacco users and that they substitute VERVE® for one of the other tobacco products. For some study participants, there is a reduction in combusted tobacco use. While for most, the reduction in CPD is modest, there was a small number of participants who reported reducing CPD by 50% or more. The studies also showed a small number of smokers who completely stopped cigarette use. Again, these numbers are small, but the studies themselves were of limited duration and there are limitations to actual use studies (e.g., participants receive the product for free). The products were available to consumers in a limited market which precludes the potential for epidemiological studies on nationally representative population data for the products prior to the submission of the PMTAs; nation-wide survey data on tobacco use would not have picked up this limited marketing and therefore would not provide information on VERVE® use. The MACS provided real-world assessment through in-market survey evaluations. If the VERVE® products were to be commercially available, then nationally representative population data may be obtainable and would provide greater insight into the potential for smokers to either switch completely to VERVE® products or to significantly reduce the use of combusted tobacco products. The data supplied by the applicant does not indicate that the availability of the VERVE® products would significantly increase tobacco use, especially by non-users, former smokers, or youth. Therefore, the benefit to current smokers or tobacco users of VERVE® in the marketplace, albeit small, is not likely to be outweighed by risks that nonusers, including youth, would start using VERVE® and then possibly other more hazardous tobacco products.

It is important to consider the relative strength and quality of data sources provided to support an understanding of new tobacco product use among current tobacco users. The actual use study provides direct evidence of new tobacco product use from a prospective clinical study. Results from the applicant's AUS are comparable to clinical studies of smoking cessation with NRT (*i.e.*, a comparable proportion of dual users and non-users of VERVE® products report use of NRT to quit smoking, indicating that VERVE® users are similarly likely to pursue smoking cessation measures (50)). The MAC study is an observational, cross-sectional (data collected at one point in time only) study which utilized retrospective exposure assessment (*i.e.*, participant recall of past tobacco use behaviors). Participants in both studies were current tobacco users who either expressed interest in the new tobacco product (AUS) or had already ever-used the new tobacco product (MACS) and who had no intention to quit smoking. The AUS is likely an upper-bound estimate of actual product switching given free product availability, daily/weekly diary completion requirement to continued participation, and high-interest in the product as an enrollment criterion. The MAC study provides information about observed tobacco use behaviors in a limited test market area and may represent a lower-bound estimate given the absence of a comprehensive, national marketing plan and non-probabilistic recruitment strategy *(i.e.*, respondents to the applicant's user survey).

2.6. Product Labeling, Consumer Comprehension, and Marketing Plan

2.6.1. Proposed PMTA Labeling

The applicant submitted specimens of proposed labeling for the four VERVE® products in section 4 of the PMTAs. OCE DPAL reviewed these specimens of proposed labeling and concluded that there is no evidence to suggest that the labeling is false or misleading at this time.

As TPL, I agree with OCE DPAL's review that there is no concern regarding false or misleading statements with the proposed labeling.

2.6.2. Consumer Perception and Understanding of Risk

The PMTAs included two consumer perception studies regarding the promotional materials and consumer understanding, and a use study that examined consumer perception. The social science review evaluated relevant information regarding consumer absolute and relative risk perceptions and consumer understanding in the context of viewing VERVE® and their promotional materials (Risk Perceptions Study and PBI Study) or using VERVE® (MACS).

Absolute Risk Perceptions. From the Risk Perception Study, the applicant reported absolute risk perceptions before and after viewing VERVE® promotional materials. The social science review noted that the Risk Perception Study is a qualitative study where the applicant provides frequency counts of themes mentioned by the participants. The majority of participants, regardless of tobacco user status, responded that there was a risk of negative impact to health (52% before, 61% after viewing VERVE® promotional materials), nicotine addiction (81% before, 83% after), and harm to baby if pregnant or nursing (60% before, 73% after). Approximately half of the participants believed there was a risk of mouth cancer (49% before, 49% after) and discolored teeth or decay (47% before, 42% after). Fewer participants believed there was a risk of lung cancer (23% before, 27% after), heart disease/heart attack (34% before, 54% after), and harm to someone nearby (3% before, 3% after). The applicant assessed these perceptions at the brand level; however, it also asked a question to assess whether risk perceptions would change for other variations of the products. The applicant reported that 96.8% of all participants said their response would be the same.

In the PBI Study, the applicant assessed absolute risk perceptions before and after full (viewed all promotional materials (i.e., 30-second advertisement, compilation of print marketing materials) as well as a picture of the four VERVE® products) and reduced (viewed a picture of the four VERVE® products) exposure to promotional materials. Participants rated absolute risk of using VERVE® every day (0% "extremely unlikely" to 100% "extremely likely") for the following health effects: risk of harming health, mouth cancer, lung cancer, heart disease/heart attack, nicotine addiction, discolored teeth or decay, harm to baby if pregnant or nursing, worsens an existing illness, trouble catching breath, bad cough, and harming someone nearby. The applicant also assessed absolute risk of smoking cigarettes every day for the health effects and compared post-test mean scores using paired t-tests to see if risk perceptions differed significantly. Nicotine addiction was the highest VERVE® absolute risk perception before and after viewing promotional materials in both exposure conditions, and mean scores ranged from 56.84% to 79.62%. Participants in all subgroups perceived the risks of harming health, mouth cancer, lung cancer, heart disease/heart attack, nicotine addiction, discolored teeth or decay, harm to baby if pregnant or nursing, worsens existing illness, trouble catching breath, bad cough, and harming someone nearby associated with smoking cigarettes every day as statistically significantly greater than using VERVE® every day ($p < 0.001$).

From the MACS, the plurality of current users rated VERVE® as "slightly harmful" (37%) or "not at all harmful" (27%). In contrast, the plurality of past triers and users responded "don't know" (43%).

Relative Risk Perceptions. From the Risk Perception Study, the applicant assessed VERVE® risk perceptions relative to daily use of cigarettes, smokeless tobacco products, e-vapor/e-cigarettes products, FDA-approved over-the-counter smoking cessation medication, and completely quitting all tobacco use. Risk perceptions were measured on a scale of 0 (no risk to health) to 7 (great risk to health) both before and after viewing VERVE® promotional materials. Changes before and after viewing were

miniscule, so the social science review provided after-viewing scores only. The applicant also provided scores for each user group separately in its report, but the social science review provided scores for the whole sample. All participants rated VERVE® 4.4 (SD, 2.0), which is a bit higher than the midpoint, indicating a perception of risk similar to that of e-vapor/e-cigarettes and less than smokeless tobacco. Compared to VERVE®, participants rated smoking cigarettes as the greatest risk (6.7, SD 0.74), followed by smokeless tobacco (5.7, SD 1.51), e-vapor/e-cigarettes (4.5, SD 1.93), smoking cessation medication (2.5, SD 1.84), and quitting all tobacco use (0.4, SD 1.02).

From the PBI Study, all tobacco user and non-user subgroups in both full and reduced exposure conditions rated smoking cigarettes and using smokeless tobacco daily as higher risk than using VERVE® and completely quitting all tobacco and never using tobacco as less risk than using VERVE®. The applicant provided z-scores and all p values were significant at the $p < 0.001$ level. All tobacco user and non-user subgroups in both conditions perceived that smoking cigarettes has higher risk of harming one's health, mouth cancer, lung cancer, heart disease/heart attack, nicotine addiction, discolored teeth/decay, harm to baby if pregnant or nursing, worsens existing illness, trouble catching breath, bad cough, and harming someone nearby compared to using VERVE® ($p < 0.001$). There were no significant differences in perceived relative risk across all four varieties of VERVE® products in all subgroups in both conditions.

From the MACS, the majority of current users and past triers/users perceived VERVE® as "less harmful" than smoking cigarettes (75% and 63%, respectively) and using smokeless tobacco products (63% and 68%, respectively). A little over a third of current users and past triers/users rated VERVE® as "less harmful" than e-cigarettes (42% and 35%, respectively). The majority of current users and past triers/users rated VERVE® as having "about the same" harm as smoking cessation aids (58% and 56%, respectively). Lastly, relative risk perceptions were mixed regarding quitting and not using any other tobacco products. Current users rated VERVE® as either "less harmful" (35%), "about the same" harm (33%) or "more harmful" (23%) while the majority of past triers/users rated them as "more harmful" (52%) or "don't know" (16%).

Understanding Risk Summary

Data from the Risk Perception Study, the PBI Study, and the MACS show that participants believe the VERVE® products are not risk-free. The majority of participants from the Risk Perception Study and the PBI Study also indicated that "nicotine addiction" was the highest health risk for using VERVE® every day. Also, participants from all three studies rated cigarette smoking as higher risk than using VERVE®. From the literature, there are mixed findings regarding risk perceptions of oral nicotine-containing products; however, the studies all indicate that participants agree that these oral nicotine-containing products are not risk-free.

The social science review noted that data from all three studies are at the brand level; however, some format and flavor data are presented from the Risk Perception Study and PBI Study. First, the Risk Perception Study included a question asking participants to indicate whether they would respond to additional risk perceptions questions the same way regardless of VERVE® format and flavor. Though they were not probed about each specific format and flavor, participants did respond that they would answer the questions the same way. More specifically, relative risk data is presented for each format and flavor subject to these PMTAs in the PBI Study. There were no significant differences across formats and flavors. Based on the submitted data, this review identifies no concerns with the presented findings and results regarding consumer understanding of risk.

The social science review concluded that based on the data submitted by the applicant, there are no identified concerns with the findings of the Risk Perception Study, the PBI Study, and the MACS. And

therefore, there are no concerns with the results of these studies regarding consumer understanding of risk.

As TPL, I agree with the social science review that there are no identified concerns regarding consumer perception and understanding of risk for the four VERVE® products.

2.6.3. Marketing Plan

Per the OHCE consult, the applicant submitted marketing information as part of the subject applications in *Section 4. Specimens of Labeling* (pp. 1-4). OHCE's review notes that the information provided in the applicant's proposed marketing plan is broad and incomplete. The applicant states that it intends to market its products to adult tobacco consumers (ATC), and specifically, to adult smokers (AS). However, the applicant does not describe plans to target its audience by other demographic characteristics (e.g., race/ethnicity, geographic region), psychographic characteristics, or behaviors other than current tobacco use, and the applicant does not specify how it intends to target and reach ATC/AS aged 21+. Additionally, it is unclear if the marketing information provided by the applicant covers the full extent of the applicant's plan. For example, the applicant omits discussion of several marketing channels and tactics (e.g., broadcast TV; digital radio; billboards and similar out-of-home media; sponsorships). OHCE's review raised concerns about the potential broad reach of the applicants marketing, absent more robust targeting controls, to adults aged 18+ (instead of adults of the federal minimum legal age of sale of tobacco products) and youth. OHCE concluded that if the products are authorized to be marketed, FDA should place restrictions on digital marketing and TV and radio marketing to protect youth. Additionally, OHCE recommends that any MGO letter encourage the applicant to take additional steps to limit youth exposure to print and point-of-sale advertising, including, for example, limiting advertising to print publications where 85% or more of the readership is 21 years of age or older and/or selecting publications that do not over-index for youth. The applicant includes information about its intended use of warnings, ingredients, and health information as part of its products' labeling but does not describe key message themes it intends to use in its labeling, advertising, marketing, or promotional materials to target ATC/AS or the goals of such marketing materials. Understanding the key message themes of the new products will enable better insight regarding the potential impact of the advertising on youth appeal. OHCE recommends that if these applications will be the subject of MGOs then the applicant should submit 30-day advance notifications of marketing materials for a period for time.

As TPL, I agree with the OHCE consult that the marketing granted order should include the recommended marketing requirements and restrictions. In addition, I agree with OHCE to include recommendations for the applicant to limit youth exposure to print and point-of-sale advertising.

3. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Dr. Luis Valerio on August 4, 2020. The FONSI was supported by an environmental assessment prepared by FDA on August 4, 2020.

4. CONCLUSIONS AND RECOMMENDATIONS

Based on the data received to date, the following U.S. Smokeless Tobacco Company LLC premarket tobacco product applications **do** contain sufficient information to show that marketing of the new products would be appropriate for the protection of the public health and support marketing orders under section 910(c) of the FD&C Act:

As discussed in Sections 2.3 through 2.6 of this review, I recommend the PMTAs be authorized. None of the grounds specified in Section 910(c)(2) of the FD&C Act apply. Specifically, I find the following:

1. Permitting the marketing of the new products in accordance with the requirements in the marketing granted orders is appropriate for the protection of the public health, as described in Section 910(c)(4) of the FD&C Act;

2. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in 906(e);

3. Based on a fair evaluation of all material facts, the labeling is not false or misleading in any particular; and

4. The products do not fail to conform to a tobacco product standard in effect under Section 907 of the FD&C Act.

I recommend FDA grant marketing authorization for the products described in the following STNs:

1. PM0000470 – VERVE® Discs Blue Mint
2. PM0000471 – VERVE® Chews Blue Mint
3. PM0000472 – VERVE® Discs Green Mint
4. PM0000473 – VERVE® Chews Green Mint

The new products are authorized with a (b) (4) shelf life. The applicant may provide updated data on production batches to propose an extension of shelf life as part of annual post market reporting.

4.1 Discussion

The PMTAs included inadequate information on the manufacturing processes (e.g., missing SOPs, detail for the order of adding ingredients); however, during the inspection FDA received adequate information to demonstrate that the four VERVE® products can be manufactured in a consistent manner. FDA verified the levels of seven HPHCs (acetaldehyde, arsenic, cadmium, formaldehyde, nicotine, NNN, and NNK) and the results were similar, with the exception of increased arsenic (14% higher) in the VERVE® Chews and increased free nicotine (2357% higher) in the VERVE® Discs, both in comparison to the data in the PMTAs. Both increases were determined to not be of concern based on the toxicology and BCP reviews, respectively. Arsenic measured VERVE® Chews is less than or tantamount to arsenic measured in all comparator products and well below the established reference (RfD) or acceptable oral dose for arsenic. The increase in measured free nicotine in unlikely to result in increased abuse liability.

The results of the toxicology evaluation, along with the ingredient and HPHC information, demonstrate that the toxicity potential of the VERVE® products is lower than cigarettes and smokeless tobacco, and likely similar to that of NRT. If a smoker were to switch from cigarettes to VERVE® products, the toxicological evaluation supports the assertion that the consumer would have much less HPHC exposure compared to Marlboro 100's cigarettes and General Snus (Appendix Table 16). The non-tobacco ingredients do not present a toxicological concern because exposure to these ingredients from use of the VERVE® tobacco products is tens to thousands of times lower than the respective toxicity reference values. Together, this information indicates that the VERVE® products likely present a lower public health concern for tobacco-related diseases. This is predicated based on switching from cigarettes to the VERVE® products, which the limited data in the applications does not indicate is likely. This is supported by the literature research on oral tobacco products. Further, a significant decrease in CPD (i.e., 50% or

greater), or substituting VERVE® products for a smokeless tobacco with polytobacco use could also have the potential to decrease tobacco-related diseases.

Based on the applicant's clinical studies, the VERVE® products have reduced abuse liability when compared to the study subjects' UB cigarettes, as indicated by the lower plasma nicotine concentrations and lower positive subjective ratings. This also supports a reduction in the likelihood that youth, non-smokers, or former smokers would initiate or reinitiate tobacco use with the VERVE® products. The reduced subjective appeal, however, may prevent current smokers from switching completely to the VERVE® products. The submitted studies suggest that few smokers (11%) switch completely to VERVE® or other oral tobacco products, but these data are based on one week of VERVE® use and do not reflect the measured decline in VERVE® acceptability among smokers that was captured in the applicant's 12-week actual use study for a prior version of VERVE® Discs Blue Mint (Gen 1). Therefore, the percentage of complete switching would likely be lower than the identified percentage in the applicant's study. However, this does not impact the finding that VERVE® products should be granted a marketing order because the applicant has demonstrated a health benefit for the small percentage of smokers who completely switch. Dual or poly use is the primary use behavior expected of VERVE® product users. Smokers who dual use VERVE® products with cigarettes, and do not substantially reduce their CPD (i.e., by 60% or greater), do not reduce their exposure to nicotine or non-nicotine BOE. However, even a modest reduction in daily cigarette consumption may reduce the risk of tobacco related disease due to decreased exposure to HPHCs.

In terms of youth risk, the information extrapolating dissolvable tobacco products to VERVE® from the literature and from national survey data support that there is low likelihood of youth initiating tobacco use with the new products. Nonetheless, given the strong evidence regarding the impact of youth marketing exposure to youth appeal and initiation of tobacco use, a marketing authorization should include postmarket requirements to help ensure that youth exposure to tobacco marketing is limited.

While there were no clinical studies conducted specifically to evaluate the health effects of VERVE® products, alone or in combination with other tobacco products, there were limited data on consumer or study subject reports of any AEs. The five clinical studies had a combined total of 253 participants and 144 AEs reported. AEs assessed as likely or possibly related to the use of VERVE® products comprised 29.7% of all reported AEs. All 27 AEs deemed likely or possibly related to the use of VERVE® products were considered mild. There were no severe or serious AEs reported. Although clinical studies designed specifically to address the potential health effects of the VERVE® products would have strengthened the PMTAs, the ingredients and ingredient levels in the products and HPHC measurements and comparisons to cigarette smoke and smokeless tobacco support the determination that use of the VERVE® products in place of smoking or combined with a significant (i.e., 50% or greater) decrease in CPD, would decrease exposures to HPHCs and likely decrease the occurrence of tobacco-related disease. Though complete substitution of cigarettes with VERVE® products or ≥ 50% decrease in CPD with poly use is unlikely, a modest reduction in daily cigarette consumption may reduce the risk of tobacco related disease due to decreased exposure to HPHCs.

The public health benefit of the VERVE® products is attributed to the ingredients and HPHC levels. This benefit, however, is predicated on the use of the VERVE® products in place of cigarettes or in place of a significant portion of a smoker's CPD. The PMTAs indicate that VERVE® is only moderately appealing among current tobacco users, and these users seem to have moderate intentions to try, to use, and to switch to VERVE®. The PMTAs do indicate a small number of subjects who switched from cigarettes to VERVE® and some tobacco users continued use even though self-reporting actual quitting after using VERVE® during a 6-week study period. While the number of tobacco users who would alter their tobacco use due to the use of VERVE® sufficiently to benefit from the decreased HPHC exposures is small, the

minimal HPHC exposure could positively impact health benefits for those tobacco users and for others who are near them regularly (e.g., children); use of VERVE® products is not associated with significant second-hand exposure which decreases disease risks for the general population.

4.2 Recommendation for Marketing

A marketing granted order should be issued for the new tobacco products subject of this review, as identified on the cover page of this review.

The following language will be included in the marketing authorization:

> Based on our review of your PMTAs, we determined that the new tobacco products, as described in your applications and specified in Appendix A, are appropriate for the protection of public health. It should be noted that our determination that the marketing of these products is APPH is based on the submitted microbial stability data[14]. The issuance of these marketing granted orders confirms that you have met the requirements of section 910(c) of the FD&C Act and authorizes marketing of your new tobacco products. Under the provisions of section 910, you may introduce or deliver for introduction into interstate commerce the tobacco products, in accordance with the marketing order requirements outlined in these orders, including all appendices.

14. [14] The data provided support microbial stability of the products over (b) (4) . The stability data for (b) (4) is acceptable and there are no other stability concerns. If you would like FDA to evaluate additional microbial stability data for a longer period, submit this information in a post-market report.

5. ACRONYMS

AE	adverse events
ALCS	Altria Client Services, LLC
APC	aerobic plate counts
$AUC_{0\text{-}t}$	area under the nicotine concentration-time curve
a_w	water activity
BCP	Behavioral and Clinical Pharmacology
BIMO	Bioresearch Monitoring
(B)LOQ	(below) limit of quantitation
BOE	biomarkers of exposure
BOPH	biomarkers of potential harm
CAS number	Chemical Abstracts Service number
CDC	Centers for Disease Control and Prevention
Cfu	colony forming unit
C_{max}	maximum measured plasma nicotine concentration
CO	carbon monoxide
COHb	blood carboxyhemoglobin
CPD	cigarettes per day
CPSC	Consumer Product Safety Commission
CRT	Center for Research and Technology
CTP	Center for Tobacco Products
DPAL	Division of Promotion, Advertising, and Labeling
EIR	Establishment Inspection Report
ENDS	electronic nicotine delivery systems
FD&C Act	Federal Food Drug and Cosmetic Act
FDA	Food and Drug Administration
FONSI	finding of no significant impact
FTCD	Fagerström Test for Cigarette Dependence
GRAS	generally recognized as safe
HPHC	Harmful and Potentially Harmful Constituents
ISO	International Organization for Standardization
M	Month
N/A	not applicable
NAB	N-nitrosoanabasine
NAT	N-nitrosoanatabine
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	n-nitrosonornicotine
NRT	nicotine replacement therapy
NST	novel smokeless tobacco
OCE	Office of Compliance and Enforcement
ORA	Office of Regulatory Affairs
OS	Office of Science
OSHA	Occupational Safety and Health Administration
PET	polyethylene terephthalate
PK	Pharmacokinetic
PMTA	premarket tobacco application
RfD	reference dose

RH	relative humidity
RSD	relative standard deviation
SAE	serious adverse event
SD	standard deviation
SFFL	Southeast Food and Feed Laboratory
SOP	standard operating procedure
S-PMA	S-phenylmercapturic acid
STL	Southeast Tobacco Laboratory
STN	Submission Tracking Number
$T_{1/2}$	apparent first-order terminal nicotine elimination half-life
T_{max}	time of the maximum measured plasma concentration
TNE	total nicotine equivalent
TPL	Technical Project Lead
TPMF	Tobacco Product Master File
TSNA	tobacco-specific nitrosamines
UB	usual brand
UB-NCC	usual brand-normal nicotine content
USSTC	US Smokeless Tobacco Company
USSTP	US Smokeless Tobacco Products, LLC
VAS	visual analog scale
VLNC	very low nicotine content

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7. APPENDIX A

Table 13: Ingredients other than tobacco for cross-referenced PMTA submissions

Product Name	Ingredients	Breakout of Ingredient	Target Weight (mg/piece)
PM0000470 VERVE® Discs Blue Mint	Single and complex+ ingredients	(b) (4)	
	(b) (4) +		
PM0000471 VERVE® Chews Blue Mint	Single and complex+ ingredients		

Product Name	Ingredients	Breakout of Ingredient	Target Weight (mg/piece)
		(b) (4)	
	(b) (4)		
	(b) (4)		
	(b) (4)		
	(b) (4)		
	(b) (4)		
PM0000472 VERVE® Discs Green Mint	Single and complex+ ingredients		

Product Name	Ingredients	Breakout of Ingredient	Target Weight (mg/piece)
		(b) (4)	
	(b) (4)+		
	(b) (4)+		
PM0000473 VERVE® Chews Green Mint	Single and complex+ ingredients		
	(b) (4)		

Product Name	Ingredients	Breakout of Ingredient	Target Weight
	(b) (4)		

+ Complex purchased ingredients

Table 14: Total ingredients for cross-referenced PMTA submissions

Product Name	Ingredients	Total Quantity per Piece (mg/piece)	Total Quantity per Gram of Each Piece (mg/g)	Quantity as Percent of Total Weight per Piece (%)
PM0000470 VERVE® Discs Blue Mint	(b) (4)			
PM0000471 VERVE® Chews Blue Mint				
PM0000472 VERVE® Discs Green Mint				
PM0000473 VERVE® Chews Green				

Product Name	Ingredients	Total Quantity per Piece (mg/piece)	Total Quantity per Gram of Each Piece (mg/g)	Quantity as Percent of Total Weight per Piece (%)
Mint	(b) (4)			

Table 15: Comparison of HPHC levels in the new products to Nicorette gum, General Snus, and cigarettes (per portion basis)

Constituent	New Products		Comparator Products			% Change[a]		
	VERVE® Discs	VERVE® Chews	Nicorette® Fresh Mint™ Gum	General Snus[15,16]	Cigarettes[17] (Marlboro 100's Box)	Nicorette Gum	General Snus	Cigarettes
Nicotine (total), mg/portion	1.33-1.45	1.33-1.54	2.02 (2.00-2.05)	10.915	2.59	↓25	↓86	↓41
Nicotine (free), mg/portion	0.31-0.58	0.01-0.08	2.00 (1.98-2.03)	5.03**15**	N/A	↓71	↓88	
pH	7.50-7.86	5.95-6.79	10.03 (10.0-10.07)		N/A	↓22		
Cadmium, ng/portion	5.60-12.15	N/D	50.7 (45.0-55.2)	179.2216[+]	114	↓78	↓93	↓89
Arsenic, ng/portion	N/D	**22.88-24.16**	47.3 (44.4-49.6)	74.6316[+]	**11.3**	↓51	↓68	**↑114**
Benzo[a]pyrene, ng/portion	N/D	N/D	N/D		20.5			
NNN, ng/portion	0.66-1.48	N/D	N/D	108015	284		↓100	↓99
NNK, ng/portion	0.33-0.39	BLOQ	N/D	30415	145		↓100	↓100
Formaldehyde, µg/portion	0.16-0.86	0.36-0.60	BLOQ	5.5515	91.2		↓85	↓99
Acetaldehyde, µg/portion	0.09-0.76	0.30-0.57	BLOQ	20.715	1690		↓96	↓100
Crotonaldehyde, µg/portion	N/D	N/D	N/D	0.68515	59.2			

Bold text denotes that the % change is higher than 10%.

N/D = not detected; BLOQ = below LOQ; N/A = not applicable

[+] The reported values were obtained from Appendix C for General Original Portion of the Borgerding et al. publication16 and converted from ng/g of dry basis to ng/portion using the moisture content reported as 50.9% and 1 g per portion. The dry basis weight = 1 g – 0.509 g = 0.491 g. For example, cadmium (ng/portion) = 365 ng/g dry basis x 0.491 g = 179.215 ng/portion.

[a] % Change = ([Maximum constituent limit in VERVE® product (all batches, mg/portion) – [Maximum constituent limit in comparator product (mg/portion)])/[Maximum constituent limit in comparator product (mg/portion)]

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Table 16: Comparison of HPHC levels in the VERVE® products compared to Nicorette Gum, General Snus, and Cigarette (wet weight basis)

Constituent	New Products		Comparator Products			% Change[a]		
	VERVE® Discs	VERVE® Chews	Nicorette® Fresh Mint™ Gum	General Snus[9,10]	Cigarettes[11] (Marlboro 100's Box)	Nicorette Gum	General Snus	Cigarettes
Nicotine (total), mg/g	**2.50-2,78**	0.63-0.73	2.02 (2.00-2.05)	10.9[9]	2.59	**↑36**	↓75	↑7
Nicotine (free), mg/g	0.58-1.11	0.01-0.04	2.00 (1.98-2.03)	5.03[9]	N/A	↓45	↓78	
pH	7,50-7,86	5,95-6.79	10,03 (10,0-10,07)		N/A	↓22		
Cadmium, ng/g	10.77-22.92	N/D	50.7 (45,0-55.2)	179.22[10+]	114	↓58	↓87	↓80
Arsenic, ng/g	N/D	10.69-11.51	47.3 (44.4-49.6)	74.63[10+]	11.3	↓77	↓85	↑2
Benzo[a]pyrene, ng/g	N/D	N/D	N/D		20,5			
NNN, ng/g	1.25-2,85	BLOQ	N/D	1080[9]	284		↓100	↓99
NNK, ng/g	0.63-0.74	BLOQ	N/D	304[9]	145		↓100	↓99
Formaldehyde, µg/g	0.304.66	0.17-0.29	BLOQ	5.55[9]	91.2		↓70	↓98
Acetaldehyde, µg/g	0.16-1.16	0.16-0,27	BLOQ	20.7[9]	1690		↓94	↓100
Crotonaldehyde, µg/g	N/D	N/D	N/D	0.685[9]	59.2			

Table source: Internally generated based on applicant-submitted data

N/D = not detected; BLOQ = below LOQ; N/A = not applicable

[+] The reported values were obtained from Appendix C for General Original Portion of the Borgerding et al. publication[4] and converted from ng/g of dry basis to ng/g using the moisture content reported as 50.9% and 1 g per portion. The dry basis weight = 1 g – 0.509 g = 0.491 g. For example, cadmium (ng/portion) = 365 ng/g dry basis x 0.491 g x 1 g/portion= 179.215 ng/g

[a] % Change = ([Maximum constituent limit in VERVE® product (all batches, unit/g of product)] – [Maximum constituent limit in comparator product (unit/g of product)])/[Maximum constituent limit in comparator product (unit/g of product)]

Table 17: HPHCs of VERVE® products and other smokeless tobacco products

Constituent	New Products		FDA Internal Data[+]				% Change[a]			
	VERVE® Discs	VERVE® Chews	Chewing Tobacco	Dissolvables	Moist Snuff	Snus	Chewing Tobacco	Dissolvables	Moist Snuff	Snus
Nicotine (total), mg/g	2.50-2.78	0.63-0.73	8-14	8-11	11-12	9-12	↓80	↓75	↓77	↓77
Nicotine (free), mg/g	**0.58-1.11**	**0.01-0.04**	0.04-0.07	1-2	3-4	4-6	**↑1486**	↓45	↓72	↓82
pH	**7.50-7.86**	**5.95-6.79**	5.6-6.1	6.9-8.1	7.67.8	8· 8.5	**↑29**	↓3	↑1	↓8
Cadmium, ng/g	10.77-22.92	N/D	400- 500	300-600	500-560	200-400	↓99	↓100	↓99	↓99
Arsenic, ng/g	N/D	10.69-11.51	10-420	120-200	180-230	90 -130	↓97	↓94	↓95	↓91
Benzo[a]pyrene, ng/g	N/D	N/D	5-6	68-105	42 -58	1-1.7				
NNN, ng/g	1.25-2.85	BLOQ	590-667	1004-6795	3025-3748	500-1053	↓100	↓100	↓100	↓100
NNK, ng/g	0.63-0.74	BLOQ	120 -167	666-7577	953-1135	175-325	↓100	↓100	↓100	↓100
Formaldehyde, µg/g	0.30-1.66	0.17 -0.29	4.08-7.23	2.16 -6.94	0.4-1.7	5.7-8.4	↓77	↓76	↓2	↓80
Aceta ldehyde, µg/g	0.16-1.16	0.16-0.27	2-2.8	2.51-3.44	1-6	11-15	↓59	↓66	↓81	↓93
Crotonaldehyde, µg/g	N/D	N/D	-	-	0.07 - 0.08	1.0-3.4				

[+] FDA internal data obtained from Appendix B of the "FDA Testing for PMTA Norms and Triggers" memo (M:\PMTA Reviews\USSTC_PM0000470-PM0000473\STL consult memo\FDA Testing for PMTA_Norms and Triggers_DPS.pdf)

[a] % Change = ([Maximum constituent limit in VERVE® product (all batches, unit/g of product)] – [Maximum constituent limit in comparator product (unit/g of product)])/[Maximum constituent limit in comparator product (unit/g of product)]

Table 18. Constituents of VERVE® Chews and Discs products over a 12-month period

PMTA	Constituent	Mean Average Across 3 Lots with (Standard Deviation)				% Change [a] (T=6M from T=1M)	% Change [b] (T=12M from T=1M)
		T = 1M	T = 6M	T = 12M	N[1]		
PM0000470 (VERVE® Discs Blue Mint)	Nicotine (total), mg/portion	1.37 (0.02)	1.38 (0.01)	1.33 (0.02)	21	↑1	↓3
	Nicotine (free), mg/portion	0.55 (0.11)	0.38 (0.01)	0.31 (0.04)	21	↓31	↓44
	pH	7.85 (0.16)	7.59 (0.03)	7.50 (0.06)	21	↓3	↓4
	Cadmium, ng/portion	8.55 (0.28)	6.35 (1.13)	**12.15 (6.90)**	21	↓26	↑42
	Arsenic, ng/portion	N/D	N/D	N/D	21		
	Benzo[a]pyrene, ng/portion	N/D	N/D	N/D	21		
	NNN[+], ng/portion	0.66 (0.06)	0.95 (0.15)	0.74 (0.15)	21	↑44	↑12
	NNK[++], ng/portion	0.38	0.38 (0.05)	**0.39 (0.09)**	21	0	↑3
	NAB[*], ng/portion	N/D	0.47	N/D	21		
	NAT[**], ng/portion	N/D	0.33 (0.03)	N/D	21		
	Formaldehyde, µg/portion	**0.86 (0.51)**	0.56 (0.08)	**0.17 (0.05)**	21	↓35	↓80
	Acetaldehyde, µg/portion	**0.35 (0.35)**	**0.29 (0.08)**	0.12 (0.01)	21	↓17	↓66
	Crotonaldehyde, µg/portion	N/D	N/D	N/D	21		
PM0000471 (VERVE® Chews Blue Mint)	Nicotine (total), mg/portion	1.35 (0.07)	1.47 (0.03)	1.33 (0.05)	21	↑9	↓1
	Nicotine (free), mg/portion	**0.05 (0.02)**	**0.03 (0.01)**	0.01 (0.00)	21	↓40	↓80
	pH	6.62 (0.2)	6.27 (0.14)	5.95 (0.06)	21	↓5	↓10
	Cadmium, ng/portion	N/D	N/D	N/D	21		
	Arsenic, ng/portion	23.35 (0.81)	22.43 (0.26)	22.44 (0.37)	21	↓4	↓4
	Benzo[a]pyrene, ng/portion	N/D	N/D	N/D	21		
	NNN[+], ng/portion	N/D	N/D	N/D	21		
	NNK[++], ng/portion	BLOQ	BLOQ	BLOQ	21		
	NAB[*], ng/portion	N/D	N/D	N/D	21		
	NAT[**], ng/portion	N/D	1.21	N/D	21		
	Formaldehyde, µg/portion	0.43 (0.01)	0.36 (0.02)	0.43 (0.03)	21	↓16	0
	Acetaldehyde, µg/portion	0.33 (0.06)	0.43 (0.02)	0.49 (0.09)	21	↑30	↑48
	Crotonaldehyde, µg/portion	BLOQ	N/D	N/D	21		
PM0000472 (VERVE® Discs Green Mint)	Nicotine (total), mg/portion	1.42 (0.04)	1.45 (0.03)	1.32 (0.03)	21	↑2	↓7
	Nicotine (free), mg/portion	0.58 (0.06)	0.44 (0.03)	0.33 (0.01)	21	↓24	↓43
	pH	7.86 (0.10)	7.65 (0.05)	7.54 (0.03)	21	↓3	↓4

PMTA	Constituent	Mean Average Across 3 Lots with (Standard Deviation)				% Change [a] (T=6M from T=1M)	% Change [b] (T=12M from T=1M)
		T = 1M	T = 6M	T = 12M	N[1]		
	Cadmium, ng/portion	**7.87 (1.78)**	5.76 (0.20)	**5.60 (1.15)**	21	↓27	↓29
	Arsenic, ng/portion	N/D	N/D	N/D	21		
	Benzo[a]pyrene, ng/portion	N/D	N/D	N/D	21		
	NNN[+], ng/portion	**1.27 (0.71)**	**1.48 (0.59)**	**1.32 (0.54)**	21	↑17	↑4
	NNK[++], ng/portion	0.37	**0.35 (0.10)**	**0.33 (0.07)**	21	↓5	↓11
	NAB[*], ng/portion	N/D	N/D	N/D	21		
	NAT[**], ng/portion	N/D	0.29	N/D	21		
	Formaldehyde, µg/portion	**0.86 (0.39)**	0.54 (0.08)	0.16 (0.02)	21	↓37	↓81
	Acetaldehyde, µg/portion	**0.60 (0.28)**	**0.22 (0.06)**	0.09 (0.01)	21	↓63	↓8
	Crotonaldehyde, µg/portion	N/D	N/D	N/D	21		
PM0000473 (VERVE® Chews Green Mint)	Nicotine (total), mg/portion	1.37 (0.05)	1.54 (0.05)	1.36 (0.05)	21	↑12	↓1
	Nicotine (free), mg/portion	**0.08 (0.03)**	**0.04 (0.01)**	0.02 (0.00)	21	↓50	↓75
	pH	6.79 (0.18)	6.38 (0.12)	6.09 (0.06)	21	↓6	↓10
	Cadmium, ng/portion	N/D	N/D	N/D	21		
	Arsenic, ng/portion	22.88 (0.12)	24.16 (1.43)	23.86 (1.17)	21	↑6	↑4
	Benzo[a]pyrene, ng/portion	N/D	N/D	N/D	21		
	NNN[+], ng/portion	N/D	N/D	N/D	21		
	NNK[++], ng/portion	BLOQ	BLOQ	N/D	21		
	NAB[*], ng/portion	N/D	N/D	N/D	21		
	NAT[**], ng/portion	N/D	BLOQ	N/D	21		
	Formaldehyde, µg/portion	**0.60 (0.12)**	0.49 (0.04)	0.50 (0.03)	21	↓18	↓17
	Acetaldehyde, µg/portion	0.30 (0.03)	0.39 (0.01)	0.57 (0.1)	21	↑30	↑90
	Crotonaldehyde, µg/portion	BLOQ	N/D	N/D	21		

Bold text denotes that the %RSD across lots and replicates was 20% or greater.

[+] N-nitrosonornicotine; [++] 4-(N-methyl-N- nitrosoamino)-1-(3- pyridyl)-1-butanone; [*] N-nitrosoanabasine; [**] N-nitrosoanatabine

[1] Total number of replicates across three lots (n=7 per lot) of samples analyzed to determine mean quantity per time point

N/D = not detectable; BLOQ = below LOQ; N/A = not applicable

[a] % Change = ([Constituent mean (all batches, mg/portion) at T = 6M – [Constituent mean (all batches, mg/portion) at t = 1M)])/[Constituent mean (all batches, mg/portion) at T = 1M]

[b] % Change = ([Constituent mean (all lots, mg/portion) at T = 12M] – [Constituent mean (all lots, mg/portion) at t = 1M)])/[Constituent mean (all lots, mg/portion) at T = 1M]

8. APPENDIX B

APPLICATION INFORMATION				
Applicant	U.S. Smokeless Tobacco Company LLC			
Product Manufacturer	U.S. Smokeless Tobacco Company LLC			
Submission Date	July 23, 2018	**FDA Receipt Date**	July 23, 2018	
Primary STN(s)	PM0000470	VERVE® Discs Blue Mint	☒ Single ☐ Co-Packaged **Description:** Other	
	PM0000471	VERVE® Chews Blue Mint	☒ Single ☐ Co-Packaged **Description:** Other	
	PM0000472	VERVE® Discs Green Mint	☒ Single ☐ Co-Packaged **Description:** Other	
	PM0000473	VERVE® Chews Green Mint	☒ Single ☐ Co-Packaged **Description:** Other	
Cross-referenced Submission(s)[18]	**Cross-referenced STN**	**Primary STN(s)**		
	(b)(4)	Applies to all STNs above		
Amendment(s)	**Amendment STN**	**Primary STN**	**FDA Receipt Date**	
	PM0000477	Applies to all STNs above	September 19, 2018	
	PM0000500	Applies to all STNs above	February 14, 2019	
	PM0000504	Applies to all STNs above	February 27, 2019	
	PM0000505	Applies to all STNs above	March 7, 2019	
	PM0000512	Applies to all STNs above	May 8, 2019	

NEW TOBACCO PRODUCT (SINGLE PRODUCT(S))	
STN	PM0000470
Product Name	VERVE® Discs Blue Mint
Product Category	Other
Product Sub-Category	Other
Package Type	Plastic Vial and Cap
Package Quantity	8.51 g
Characterizing Flavor	Mint
Nicotine Concentration	1.5 mg/piece
Portion Count	16 Pieces
Portion Mass	0.53 g
Portion Thickness	2.83 mm – 3.83 mm
Portion Length	13 mm – 16 mm
Portion Width	10.75 mm – 13.75 mm
STN	PM0000471

[18] The application contains a valid and active cross-reference, which contains appropriate authorization for the applicant to reference the entire file or certain sections thereof.

Product Name	VERVE® Chews Blue Mint
Product Category	Other
Product Sub-Category	Other
Package Type	Plastic Button Container
Package Quantity	25.2 g
Characterizing Flavor	Mint
Nicotine Concentration	1.5 mg/pieces
Portion Count	12 Pieces
Portion Mass	2.1 g
Portion Thickness	7.0 mm- 11.5 mm
Portion Length	18.5 mm – 21.5 mm
Portion Width	14.0 mm – 17.5 mm
STN	PM0000472
Product Name	VERVE® Discs Green Mint
Product Category	Other
Product Sub-Category	Other
Package Type	Plastic Vial and Cap
Package Quantity	8.37 g
Characterizing Flavor	Mint
Nicotine Concentration	1.5 mg/piece
Portion Count	16 Pieces
Portion Mass	0.52 g
Portion Thickness	2.83 mm – 3.83 mm
Portion Length	13 mm – 16 mm
Portion Width	10.75 mm – 13.75 mm
STN	PM0000473
Product Name	VERVE® Chews Green Mint
Product Category	Other
Product Sub-Category	Other
Package Type	Plastic Button Container
Package Quantity	25.2 g
Characterizing Flavor	Mint
Nicotine Concentration	1.5 mg/piece
Portion Count	12 Pieces
Portion Mass	2.1 g
Portion Thickness	7.0 mm – 11.5 mm
Portion Length	18.5 mm – 21.5 mm
Portion Width	14.0 mm – 17.5 mm