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