Technical Project Lead (TPL) Review: SE0000487, SE0000488, SE0000533, SE0000547

SE0000487: Skoal Smooth Mint Tobacco Stick	
Package Type	Hard Box
Package Quantity	3.7 grams
Portion Count	10 sticks
Portion Mass	240.7 mg
Portion Length	65.0 mm
Portion Width	1.47 mm
Portion Thickness	1.98 mm
Tobacco Cut Size	Not Provided
Characterizing Flavor	Mint
SE0000488: Skoal Rich Tobacco Stick	
Package Type	Hard Box
Package Quantity	3.7 grams
Portion Count	10 sticks
Portion Mass	239.9 mg
Portion Length	65.0 mm
Portion Width	1.47 mm
Portion Thickness	Not Provided
Tobacco Cut Size	Not Provided
Characterizing Flavor	None
SE0000533: Skoal Mint Tobacco Stick	
Package Type	Hard Box
Package Quantity	3.7 grams
Portion Count	10 sticks
Portion Mass	235.7 mg
Portion Length	65.0 mm
Portion Width	1.47 mm
Portion Thickness	Not Provided
Tobacco Cut Size	Not Provided
Characterizing Flavor	Mint
SE0000547: Skoal Original Tobacco Stick	
Package Type	Hard Box
Package Quantity	3.7 grams
Portion Count	10 sticks
Portion Mass	237 mg
Portion Length	65.0 mm
Portion Width	1.47 mm
Portion Thickness	Not Provided
Tobacco Cut Size	Not Provided
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	U.S. Smokeless Tobacco Manufacturing Company, LLC
Report Type	Provisional
Product Category	Smokeless Tobacco
Product Sub-Category	Dissolvable
Additional Property	Stick
Recommendation	
Issue Not Substantially Equivalent (NSE) Orders.	

Technical Project Lead (TPL):

Digitally signed by Matthew J. Walters -S
Date: 2020.05.18 09:36:41 -04'00'

Matthew J. Walters, Ph.D., MPH
CDR, US Public Health Service
Deputy Director
Division of Product Science

Signatory Decision:

☒ 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)

Digitally signed by Matthew R. Holman -S
Date: 2020.05.18 09:43:21 -04'00'

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

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1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted the following predicate tobacco product:

Product Name	C.C. Carhart's Choice
Package Type	Plastic can with plastic lid
Package Quantity	32.6grams
Tobacco Cut Size	Not Applicable
Characterizing Flavor	None

The predicate tobacco product is a loose dry snuff manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 18, 2011, FDA received 4 SE Reports from Altria Client Services Inc. (ALCS) on behalf of U.S. Smokeless Tobacco Manufacturing Company, LLC. FDA issued Acknowledgement letters on September 21, 2011 for SE0000533 and SE0000547, and on September 23, 2011 for SE0000487 and SE0000488. FDA received unsolicited amendments (SE0003961, SE0003962, SE0003901, and SE0003918) on November 4, 2011, containing corrections to the definitions included in the original reports. FDA issued Advice/Information Request letters (A/I letters) on December 17, 2012 for SE0000487 and SE0000488, and on January 2, 2013 for SE0000533 and SE0000547. FDA received responses to the A/I letters for SE0000487 and SE0000488 on January 14, 2013 (SE0006018 and SE0006019, respectively), and for SE0000533 and SE0000547 on January 25, 2013 (SE0006751 and SE0006761, respectively). On March 29, 2013, FDA issued a Notification letter, indicating that scientific review was expected to begin on May 12, 2013. On April 2, 2013, FDA conducted a telecon to request the applicant to provide additional information to identify the new and predicate products. On April 4, 2013, FDA issued a correction letter to the Notification letter, correcting how information should be submitted. On April 5, 2013, FDA received amendments for all of the SE Reports, containing the requested information (SE0008159, SE0008160, SE0008164, and SE0008166). On May 17, 2013, FDA conducted a telecon to request the applicant to provide Environmental Assessments. On May 30, 2013, FDA received an amendment containing the requested information for each SE Report (SE0008772, SE0008771, SE0008764, and SE0008767). On August 29, 2014, FDA issued an A/I letter based on scientific review. During a follow-up phone call on September 15, 2014, the applicant stated that additional clarification was needed on several of the deficiencies listed in the A/I letter before they could respond. Based upon the follow-up phone call with USSTC, FDA issued a correction letter on October 9, 2014. FDA received a response to the A/I letter (SE0010722) on October 27, 2014. The amendment includes information on the differences in the new and predicate product design parameters, packaging information, unique identification of the new and predicate product ingredients, a statement to comply with Section 910(a)(4) of the Act, and other data addressing the deficiencies. FDA then issued a Preliminary Finding letter on June 8, 2015. FDA conducted a follow-up phone call on June 12, 2015 to confirm receipt of the Preliminary Finding letter and the applicant's intent to respond. During the call, the applicant stated that additional clarification on some of the deficiencies was needed before they could agree to respond the Preliminary Finding letter. FDA made corrections as appropriate and issued a correction letter on June 16, 2015. On July 7, 2015, FDA received the applicant's response to the deficiencies (SE0012151), including a statement that the predicate product was not tested for HPHCs. The applicant identified the predicate product as C.C. Carhart's Choice for all SE Reports. The applicant also provided multiple surrogate predicate products throughout the SE Reports and in various responses to address concerns raised by FDA.

Product Name	SE Report	Amendments
Skoal Smooth Mint Stick	SE0000487	SE0003961 SE0006018 SE0008159 SE0008772 SE0010722 SE0012151
Skoal Rich Tobacco Stick	SE0000488	SE0003962 SE0006019 SE0008160 SE0008771 SE0010722 SE0012151
Skoal Mint Tobacco Stick	SE0000533	SE0003901 SE0006751 SE0008164 SE0008764 SE0010722 SE0012151
Skoal Original Tobacco Stick	SE0000547	SE0003918 SE0006761 SE0008166 SE0008767 SE0010722 SE0012151

1.3. SCOPE OF REVIEW

This review captures all regulatory, compliance, and scientific reviews completed for these SE Reports.

2. REGULATORY REVIEW

Regulatory reviews were completed by Jennifer German on December 17, 2012 and Atasi Poddar on February 6, 2013 for SE0000487 and SE0000488. Regulatory reviews were completed by Ella Yeargin on January 1, 2013 and Atasi Poddar on March 19, 2013 for SE0000533. Regulatory reviews were completed by Anna Postell on January 2, 2013 and Atasi Poddar on April 30, 2013 for SE0000547.

The final reviews conclude that the SE Reports were *not* administratively complete because the following information was not included in the SE Reports:

- Environmental Assessments

The applicant submitted Environmental Assessments on May 29, 2013, after all of the regulatory reviews were completed. Therefore, the TPL review concludes that the SE Reports are administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed a review to determine whether the applicant established that the predicate tobacco product is a grandfathered product (i.e., was commercially marketed in the United States other than exclusively in test markets as of February 15, 2007). The OCE reviews dated October 24, 2012, May 1, 2013, and March 6, 2018, conclude that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco product is grandfathered and, therefore, is an eligible predicate tobacco product.

Because the new tobacco products are not substantially equivalent to the predicate tobacco products, OCE did not complete reviews to determine whether the new tobacco products are in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as required by section 910(a)(2)(A)(i)(II) of the FD&C Act.

4. SCIENTIFIC REVIEW

Scientific reviews were completed by the Office of Science (OS) for the following disciplines:

4.1. CHEMISTRY

Chemistry reviews were completed by Shixia Feng on September 27, 2013, and December 23, 2014, and Todd Cecil on September 1, 2015.

The final chemistry review concludes that the new tobacco products have different characteristics related to chemistry compared to the predicate tobacco product and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. In your July 2015 amendment to all of your SE Reports, your responses to Deficiencies 1 and 14 in the FDA June 2015 Preliminary Finding Letter includes data representing the measured amounts of eight HPHCs of the new products and a surrogate predicate product. The HPHC data that was reported did not include the number of replicate determinations, the standard deviations of these replicates, or the validation parameters of the procedures. A full evaluation of the HPHC data is not possible without this information. Clarify the number of replicates for the reported data. If more than one replicate was performed, provide the individual values for each of the HPHC determinations, their mean, and standard deviation.

2. In your July 2015 amendment to all of your SE Reports, your responses to Deficiencies 1 and 14 in our June 2015 Preliminary Finding Letter, includes HPHC data that requires additional information in order to fully evaluate the data. In Table 1 of this amendment, you report the amount of Arsenic in all products to be below the limit of quantification (BLOQ). You also report the amount of Benzo[a]pyrene for products SE0000488, SE0000533, and SE0000547, and the amount of Crotonaldehyde for products SE0000533, SE0000547, and the surrogate product to be BLOQ. In Table 2 of this amendment, you present data that is intended to represent a typical daily exposure. However, the values that were listed as BLOQ in Table 1 are also listed as BLOQ in Table 2. It is unclear whether the data in Table 2 is representative of all of the HPHCs reported or is limited to HPHCs having a numerical value reported in Table 1. Each of the methods that you referenced in your response to Deficiency 1 of your amendment lack sufficient detail and validation data. For example, you reported data BLOQ but did not provide the limit of quantification. To adequately review your response, provide the following information for AM-187, SOP-210, AM-052, and AM-189:

    a. the complete description of the instrument used to record the reported data
    b. the step-by-step instructions for the sample preparation, standard preparation, calibration curves solutions
    c. instrument settings (such as split ratio, carrier gas, injection volume, injection type, injector temperature, temperature gradient, column type and dimensions, detector settings, etc.)
    d. validation to include precision, accuracy, specificity, limit of quantification, and limit of detection, for each analyte being measured
    e. demonstrate that the methods are suitable to report the results provided in Table 1 of your amendment.

    In addition, provide the following specific clarifications to the methods described in the amendment:

    f. The procedure titled (b) (4) – AM-052" includes a description of an (b) (4) (b) (4). In the description, the procedure states that (b) (4) " is (b) (4) (b) (4). The description does not indicate the manner in which the new product was sampled. (b) (4) has not been addressed. In order to demonstrate that the process used to manufacture the new products does not cause the new products to raise different questions of public health, provide a detailed description of the sampling procedures used to measure (b) (4) in the new product. Clarify the products used to generate the data presented in Table 1 of your responses to Deficiencies 1 and 14.

    g. In the procedure titled "Smokeless Tobacco TSNA – SOP 210", you state that the (b) (4) (b) (4). The procedure described here differs from the procedures (b) (4) described in your response to Deficiency #4. Clarify the procedure used to sample and measure the new and predicate products. Describe how the (b) (4) procedure for TSNA measurement and the (b) (4) procedures described in your October 2014 amendment are related and can be compared (See Deficiency 4 below).

3. In your July 2015 amendment to all of your SE Reports, your responses to Deficiencies 1 and 14 in our June 2015 Preliminary Finding Letter, includes HPHC data for SE0000547 that shows a difference in HPHC yields for the new and predicate product. More specifically, when the HPHC values are converted to a common unit of ng/g, the amount of acetaldehyde reported for the new product shows an increase of 44% over the surrogate product. Provide a scientific rationale as to why the higher levels of acetaldehyde in the new product do not cause the new product to raise different questions of public health.

4. In your July 2015 amendment to all of your SE Reports, your responses to Deficiencies 1 and 14 include an appendix in which the analytical procedures used to measure HPHCs are briefly described. In the description titled "(b) (4) – AM-052" you stated that the laboratory that conducted the experiment (b) (4)) was accredited to ISO17025 and was specifically accredited to perform the procedure to measure Arsenic and Cadmium. Two of the other methods (B[a]P and Carbonyls) described in the appendix were conducted in the same accredited laboratory but neither description indicates if accreditation of the procedures has been achieved for those methods. The fourth procedure (TSNA) was conducted by (b) (4) and no information about accreditation of the lab or procedure is provided. To understand the capability of the laboratories used to measure the HPHCs in the new and surrogate product, clarify the accreditation status for (b) (4) and (b) (4) and indicate whether the procedures being used in that laboratory (AM-187 and AM-189 for (b) (4) and SOP-210 fo (b) (4)) are a part of that accreditation.

5. In your July 2015 amendment to all of your SE Reports, in your response to Deficiency 4, you provided the history of two procedures that you used to measure NNN and NNK. You stated that the procedure used for the predicate product, a (b) (4) procedure, was studied and published as a (b) (4) standard procedure. You also stated that the procedure used to measure your new products, a (b) (4) S procedure, was separately studied as an updated, parallel (b) (4) standard procedure. You further stated that the (b) (4) and that the %CV was in an acceptable range and thus were equivalent. The comparison of the results of the measurements of the new and predicate product using the same procedure was not provided. The inclusion of procedures in a (b) (4) does not necessarily indicate that the procedures are comparable. In order to compare the results of the TSNA studies for the new and predicate products, provide the results of comparisons using the same procedure or the complete method comparison study using common measurements with a predetermined level of variability that is linked to the acceptance criteria for the TSNA measurements.

For all SE Reports, the applicant indicates that HPHC measurements from the predicate product are not available and that the surrogate predicate product (C.C. Carhart's Choice), a provisional variant of the predicate product (C.C. Carhart's Choice), is used for all HPHC comparisons with the new products. Based on similarity in product characteristics between the surrogate predicate product and the predicate product, the reviewer considers the use of the surrogate product appropriate for the evaluation of the HPHCs in the context of this review. While additional details and method validation information is still needed to ensure validity of the HPHC data for all new tobacco products and the surrogate predicate product, an evaluation was completed under the assumption that the data is valid. For example, SE0000547 indicates that the acetaldehyde yield from the new tobacco product is increased compared to the surrogate predicate tobacco product. If the HPHC data were valid this would be of concern since acetaldehyde is a carcinogen. Increases in HPHCs yields from the new product may consequently result in increased HPHC exposures for users of the new product compared to users of the predicate product. It is also unclear how HPHC measurements identified as BLOQ were considered in the applicant's calculations of estimated daily exposure to HPHCs from use of the new and surrogate predicate tobacco products (calculated daily exposure estimates presented in Table 2 of your July 2015 amendment). For example, did the applicant consider daily exposure to HPHCs reported as BLOQ to be zero or was the limit of quantification value used in the absence of a measured value? Also, of note, the applicant's responses to Deficiencies 1 and 14 of the Preliminary Finding Letter include an appendix in which the analytical procedures used to measure HPHCs in the new products and a surrogate predicate product are briefly described. In the description titled "Smokeless Tobacco TSNA – SOP-210", the applicant states that the (b) (4) Thus, it appears that the TSNA testing with method SOP-210 was conducted for unknown pouched tobacco products with unknown product characteristics and was not conducted on the specific new (sticks) and surrogate predicate (dry snuff) products submitted for evaluation in these SE Reports. The comparisons conducted in SE reviews evaluate differences between specific new and predicate products; they are not evaluations between the new products and other marketed tobacco products that are neither the new product nor the [surrogate] predicate product. In addition, it is unclear if the predicate product or the surrogate predicate product was used for TSNA testing. In the applicant's responses to Deficiencies 1 and 14 the applicant indicates that the surrogate predicate product is used for TSNA level comparisons with the new products, however, in their response to Deficiency 4 the applicant indicates that the predicate product is used. Clarification on whether the predicate product or the surrogate predicate product was used for TSNA testing is needed.

(b)(5) Deliberative Process Privilege

Rather, FDA needs additional information to show that the manufacturing process doesn't impact characteristics of the new tobacco products that may cause the new products raise different questions of public health, not that the manufacturing process itself raises different questions of public health. Thus, the following text will replace Deficiency 2 part f in the letter ready section of this review:

> (b) (4) (AM-052) includes a description o (b) (4) . In the description, the procedure states that (b) (4) . However, the new and surrogate predicate tobacco products are defined as (b) (4) tobacco. The description does not indicate the manner in which the new product was sampled. In addition, the description does not address th (b) (4) It is also unclear which products were tested.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a chemistry perspective.

[1] It is noted that Enthalpy Laboratory was previously Arista Laboratories – these are two names correspond to a single laboratory. This is reflected in Deficiency 4 of the letter ready section for this review.

4.2. ENGINEERING

Engineering reviews were completed by James Cheng on September 27, 2013, December 22, 2014, and September 3, 2015. An engineering memo was completed by Samantha Spindel on April 18, 2019.

The final engineering review concludes that the new tobacco products have different characteristics related to product engineering compared to the predicate tobacco product and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiency that has *not* been adequately resolved:

1. All your SE Reports fail to show that the differences in design characteristics between the new and predicate products (portioned versus non-portioned; ingested versus non-ingested; and (b) (4) versus loose dry snuff, respectively) do not cause the new products to raise different questions of public health in comparison to the predicate products. The information provided about these design differences is insufficient to demonstrate that it is appropriate and valid to perform a comparison of substantial equivalence between these product categories. The new products have the following design parameters:

    a. Tobacco particle size;
    b. Final moisture;
    c. Final portion weight;
    d. (b) (4) length;
    e. (b) (4) width;
    f. (b) (4) thickness;
    g. (b) (4) weight;
    h. (b) (4) weight;
    i. (b) (4) l length;
    j. (b) (4) l width and taper; and
    k. (b) (4) .

    In contrast, the predicate product has the following design parameters:

    l. Tobacco particle size; and
    m. Final moisture.

    To address this deficiency, provide scientific discussion and rationale as to why these dissimilarities in the design characteristics of new and corresponding predicate products do not cause the new products to raise different questions of public health. In your response, be sure to address each of the design characteristics listed above and provide adequate scientific evidence and rationale to demonstrate that these fundamental design characteristic differences do not cause the new products to raise different questions of public health.

The applicant is using a loose dry snuff tobacco product as a predicate product whereas the new tobacco products are sticks, a different sub-class of smokeless tobacco product. These two sub-classes of smokeless products have unique characteristics (portioned versus non-portioned; ingested versus non-ingested; and (b) (4) versus loose dry snuff, for the new versus predicate products, respectively) when compared to each other. The rationale provided by the applicant does not resolve the fundamental difference between the new and predicate products in that the new products are portioned by the applicant while the predicate product is portioned by the user. Design characteristics that affect portioning and portion control are important in considering whether a new product raises different questions of public health, as a difference in portion mass may affect product use behavior and user exposures. In addition, there are other differences in product characteristics that may cause the new products to raise different questions of public health in comparison to the predicate product. For example, the new products are intended to be ingested, are formed from (b) (4) (b) (4) , design characteristics that the predicate products do not exhibit.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from an engineering perspective.

4.3. MICROBIOLOGY

Microbiology reviews[2] were completed by Norma Duran on January 20, 2015 and Almaris Alonso on September 21, 2015.

The final microbiology review concludes that the new tobacco products have different characteristics related to product microbiology compared to the predicate tobacco product and that the SE Reports provide evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health.

The review identifies differences between the new and predicate tobacco products in the following parameters:

1. Fermentation times
2. Water activity
3. Addition of (b) (4)

1. Fermentation times: The applicant's manufacture process utilizes a fermentation period of (b) (4) days for the new tobacco products, whereas a fermentation period of (b) (4) days is used for the predicate tobacco product. Fermentation processes in smokeless tobacco products have been associated with formation of TSNAs like NNN and NNK, which are carcinogens. Therefore, an increased fermentation time in the new tobacco products could lead to increased formation of TSNAs and subsequently, increased TSNA exposures for users of the new tobacco products. To address this concern, the applicant provided data on the TSNA profiles during fermentation for the new and predicate tobacco products over a (b) (4) -day period. While the TSNA profile data does not indicate increases in TSNA levels at any of the timepoints for the new tobacco products, an increase in TSNA levels is seen for the predicate tobacco product between day (b) (4) of the fermentation period. Thus, the applicant reduced the fermentation period for the

[2] A microbiology review was not completed prior to the August 29, 2014, A/I letter because the SE Reports did not include microbiology information or data. However, the September 27, 2013, chemistry review identified microbiology-related deficiencies (Deficiencies 3, 9, and 13) for inclusion in the August 29, 2014, A/I letter. The January 20, 2015, microbiology review evaluated the applicant s response to these three deficiencies.

predicate tobacco product from (b) (4) days to reduce the potential for TSNA formation; a reduction in fermentation time for the new tobacco products was not necessary since TSNA increases were not indicated at any of the timepoints. Since the longer fermentation period (b) (4) for the new tobacco products, compared to that for the predicate tobacco product (b) (4) does not increase TSNA levels, the increased fermentation time for the new tobacco products does not cause the new tobacco products to raise different questions of public health.

2. Water activity: To address concerns regarding a lack of microbial stability information conveyed in FDA's PFind letter, the applicant provided microbial stability data for several parameters including water activity. The water activity of a product is a critical factor influencing whether microorganisms like bacteria, yeasts, and mold will grow, and thus is a useful measurement to predict product stability with respect to microbial growth. The applicant submitted water activity measurements at (b) (4) from the date of manufacture for one new tobacco product (SE0000488), as well as at several varying timepoints between (b) (4) from the date of manufacture for surrogate new tobacco products and a surrogate predicate tobacco product. Marlboro Smooth Mint, Marlboro Rich, Marlboro Original Tobacco, and Marlboro Cool Mint Tobacco Sticks are used as surrogates for the new tobacco products in SE0000487, SE0000488, SE0000547, and SE0000533, respectively. The surrogate predicate tobacco product (C.C. Carhart's Choice) used is a provisional variant of the predicate product (C.C. Carhart's Choice). Based on similarity in product characteristics between the surrogate new and surrogate predicate tobacco products and the new and predicate tobacco products, the reviewer considers the surrogate new and surrogate predicate tobacco products appropriate to use for the evaluation of the new and predicate tobacco products in the context of this review. The data submitted by the applicant indicates that the water activity of the new and surrogate new tobacco products is higher than that of the surrogate predicate tobacco product. A higher water activity indicates more bacteria, yeasts, and mold can grow, lowering microbial stability. However, the water activity measurements for all products at all timepoints are nearly below 0.6. Water activity values below 0.6 are not likely to support microbial growth. In addition, the water activity values are consistent with moisture content measured between 0 and 60 weeks.

   Furthermore, total aerobic microbial count (TAMC) and total yeast & mold count (TYMC) data measured for the four surrogate new tobacco products and the surrogate predicate product support that the differences in water activity do not cause the new tobacco products to raise different questions of public health. TYMC measurements for all surrogate new tobacco products were low (<10 cfu/g), and for three of the four surrogate new tobacco products, TAMC measurements were lower at week 52 than week 16 post-manufacture. In addition, all TAMC measurements for the surrogate new tobacco products are lower than the TAMC measurements for the surrogate predicate tobacco product. The highest value seen for the surrogate new tobacco products was (b) (4) cfu/g, which is approximately 100 times lower than the TAMC for the surrogate predicate tobacco product (b) (4) cfu/g). Thus, though the water activity is somewhat higher in the new and surrogate new tobacco products than in the surrogate predicate tobacco product, microbial growth is limited in the surrogate new tobacco products and their TAMC measurements are substantially lower than the TAMC for the surrogate predicate tobacco product. Therefore, the increased water activity for the new and surrogate new tobacco products, compared to the surrogate predicate tobacco product, does not cause the new tobacco products to raise different questions of public health.

3. Addition of (b) (4): The new tobacco products contain (b) (4) while the predicate tobacco product does not. The applicant states that (b) (4) is added to the new tobacco products to mitigate potential TSNA formation during fermentation and retail shelf life. (b) (4) can be reduced to (b) (4) by the same enzyme that reduces nitrate to nitrite (nitrate reductase). Because of this, high concentrations of nitrate can inhibit (b) (4) reduction and make this ingredient ineffective for its intended purpose. The applicant was asked to demonstrate the efficacy of (b) (4) to inhibit nitrate reduction or reduce TSNA formation in the new tobacco products. In the July 2015 amendment, the applicant submitted data from internal studies (i e., Chipley et al., 2005a; 2005b) to show that the addition of (b) (4) to experimental smokeless tobacco products prior to fermentation reduces nitrite and TSNA formation compared to a control smokeless tobacco product that contains no (b) (4). The internal study data also show that the addition of (b) (4) in the experimental tobacco products reduced nitrite and TSNA formation during the shelf life of the products (9 weeks) compared to the control tobacco product. In addition to these data, the applicant submitted nitrite and nitrate content of the surrogate new and surrogate predicate tobacco products over 60 weeks. Nitrite levels in the surrogate new tobacco products were BLOQ at all timepoints. The nitrate content of the surrogate new tobacco products decreased over time and was substantially lower than the nitrate content of the surrogate predicate tobacco product. When taken together, the applicant demonstrated that (b) (4) is effective in inhibiting nitrate reduction to nitrite in the new tobacco products. As a result, the addition of (b) (4) does not cause the new tobacco products to raise different questions of public health.

Therefore, the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a microbiology perspective.

4.4. TOXICOLOGY

Toxicology reviews were completed by Sheila Healy on June 17, 2014, and Roxana Weil on May 22, 2015, and December 22, 2015. A toxicology memo was completed by Roxana Weil on April 30, 2019.

The final toxicology review concludes that the new tobacco products have different characteristics related to product toxicity compared to the predicate tobacco product and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. SE0000487, SE0000488, SE0000533 and SE0000547 contained information on the consumption rate of the new products compared to the predicate tobacco products. Product consumption rates, combined with substance concentration data are essential aspects of the exposure assessment used to evaluate the potential toxicological impacts from consumer exposures to ingredients and other constituents (e.g., HPHCs) in the products under consideration. For SE0000487, SE0000488, SE0000533 and SE0000547, you assert that (b) sticks/day (approximately (b) (4) grams tobacco/day) represents "*the 90th percentile consumption*" which indicates that 90% of the users of the new products consume approximately (b) (4) grams tobacco/day, or less; and for the predicate product you provide a mean tobacco consumption rate (b) (4) grams tobacco/day. However, the data and justification you provided do not support the proposed tobacco consumption rate of approximately (b) (4) grams tobacco/day for users of your new products:

   a. The proposed consumption rate was calculated using data from th (b) (4) The proposed consumption rate of (b) sticks/day was calculated based on (b) (4) (b) (4)

(b) (4)

s.

b. You provided the study by Krautter et al. (2015) as supportive evidence for the proposed consumption rate. However, this study does not provide adequate evidence for the following reasons:

   i. The study by Krautter et al. (2015) did not allow the study participants to use tobacco sticks *ad libitum*. Due to the restrictions on product use, the tobacco stick consumption data from this study may have underestimated the true consumption rate in a population of smokeless tobacco users that use the product *ad libitum*.
   ii. Even with the restriction placed by Krautter et al. (2015) on the number of tobacco sticks study subjects were allowed to use in a day, the study reported a use rate for the tobacco sticks (mean±SD) of 6.39±4.44 sticks/day, which is higher than the consumption rate of (b) sticks/day you proposed as the 90th percentile consumption rate. Moreover, the tobacco sticks used by Krautter et al. (2015) contained 486 mg of tobacco per stick, which results in a mean tobacco use rate of approximately 3.1 grams tobacco/day (6.39 sticks/day X 486 mg of tobacco per stick), further suggesting that the proposed consumption rate of (b) sticks/day (approximately (b)(4) grams tobacco/day) significantly underestimates the total amount of tobacco that would be consumed by users of the new products.
   iii. Krautter et al. (2015) also showed that total nicotine exposure for the study subjects was consistent across users of all the tobacco products evaluated (i.e., dual use, snus, sticks, strips and orbs). Based on this study, users of the new products would consume the amount of tobacco that would result in nicotine intake levels equivalent to the nicotine intake from the predicate product. The proposed consumption rate of (b) sticks/day (b)(4) grams tobacco/day) would result in exposure to nicotine from use of your new product that is less than the nicotine exposure from the predicate product; you provided a mean consumption rate (b)(4) grams tobacco/day for the predicate product. Thus, the finding of equivalent nicotine intake in the study by Krautter et al. (2015) suggests a significantly higher usage than (b) sticks/day.

c. To support the consumption rate of (b) sticks/day for your new products, you assume that a consumer uses one tobacco stick in 15 minutes and conclude that "consumption rates higher than those reported in the extended use study are not reasonable given what is currently known about smokeless tobacco topography". Your conclusion is not supported by the information and data you provided:

   i. (b) (4) provide the following information that is relevant to the general duration and ease of use of tobacco sticks:
      - (b) (4)
   ii. You also provided the following information and assumptions that are relevant to estimating the number of tobacco sticks that could be consumed per day, based on what is currently known about smokeless tobacco topography:
      - (b) (4)
      - You estimated a total smokeless tobacco use time of 4.2 hours per day based on the study by Hatsukami et al., (1988). Therefore, the information provided on the characteristics and duration of use for the tobacco sticks, indicates that users of the new products may consume >24 tobacco sticks/day (>6 sticks/hour of tobacco use x 4.2 hours of tobacco use/day).

Taken together, the proposed (90th percentile) consumption rate of (b) sticks/day is not supported by the data, published literature and justifications you provided. Notably, the study you cited (b) (4) Published literature for mean consumption rates of other smokeless tobacco products shows a daily tobacco use range between 5.3 and 20.4 g/day [central published value of 12 g/day], which is equivalent to approximately 23 - 89 sticks of the new products per day [with a central value of 52]). Another study you cited (Hatsukami et al., [1988]) estimates a total smokeless tobacco use time of 4.2 hours per day, and additional information you provided indicates that users of the new products may be able to consume >6 sticks/hour of tobacco use. This indicates that users of the new products may consume >24 tobacco sticks/day. The data and justification you provided did not adequately demonstrate a lower tobacco use rate for the new product as compared to the corresponding predicate product. In the absence of data demonstrating a lower tobacco use rate for the new products as compared to the corresponding predicate products, the toxicological evaluation of differences between the new and predicate products in these SE Reports, the daily tobacco use for the new product is assumed to be the same as that for the corresponding predicate product. Provide adequate scientific evidence and rationale to demonstrate consumption rates of the new and predicate products, including published literature for smokeless tobacco sticks.

2. SE0000487 and SE0000533 provide justification regarding the addition of permeation enhancers (b) (4) in SE0000487 and SE0000533; (b) (4) in SE0000533) to the new products, but the submitted information does not demonstrate that the levels of these ingredients would not increase buccal permeability and uptake of HPHCs. (b) (4)

(b) (4)

(b) (4)

The effect of permeation enhancers such as (b) (4) on the uptake of compounds via the buccal mucosa depends on the concentrations and physicochemical properties of the compounds. Chemical permeation enhancers can

increase uptake of compounds via the buccal mucosa by various mechanisms, and within short exposure durations. For example, for drugs that require immediate delivery (b) (4) and (b) (4) are used to facilitate uptake across the buccal mucosa.

3. SE000547 indicates that (b) (4) (CAS (b) (4)), (b) (4) (CAS (b) (4)) and (b) (4) (CAS (b) (4)) are added to the new product but are not present in the predicate product. The information you provided did not adequately address the deficiencies on these ingredients:

   a. (b) (4) (CAS (b) (4)): You assert that the (b) (4) cut-off value used to classify Structure Category A food additives as Concern Level I (FDA, May 18, 2014) is an appropriate comparator value to evaluate exposures to this ingredient from the new product. The "Concern Level" classifications in this Guidance document are used to identify the corresponding recommendations for toxicity testing; these do not provide information on levels of oral exposures below which adverse effects are not likely to occur. For example, for compounds identified as Concern Level I (cut-off values of (b) (4) for Structure Category A additives), the referenced Guidance recommends genetic toxicity tests and short-term toxicity tests with rodents. Since these classification criteria do not provide toxicity-based reference levels protective for human oral exposures, the (b) (4) cut-off limit is not considered an appropriate comparator value to evaluate potential toxicity from human exposures to (b) (4) from tobacco product use. Evaluation of this complex flavor is more appropriately addressed based on its individual components.

      (b) (4) As discussed in detail in the deficiency above regarding your proposed consumption rate, the consumption rate of 5 sticks/day for your new products is not supported by the data and may significantly underestimate exposures from use of the new product. For smokeless tobacco, published literature supports a mean consumption rates of (b) (4) g/day of tobacco (central published value of 12 g/day), which are equivalent to approximately 23 –89 sticks per day (with a central value of 52). The level of (b) (4) in the new product from the (b) (4) may result in exposure levels that exceed the possible average daily intake (PADI) estimated by the Flavor and Extract Manufactures Association (FEMA) for flavors in foods, and the FAO/WHO Expert Committee on Food Additives (JEFCA) human intake threshold of concern for this compound. Even though these values have not been formally adopted by FDA as a standard for tobacco products, a consideration for the scientific basis of these reference values can inform the toxicological evaluation and are informative concerning whether the new products may raise different questions of public health. In addition, (b) (4) is an irritant and sensitizer, which are relevant effects for the oral mucosa given that the new products are smokeless tobacco products.

   b. (b) (4) In response to the deficiencies for these ingredients you provided exposure estimates to these compounds from product use that were calculated using the proposed consumption rate of 5 sticks/day. As discussed in detail in the deficiency above regarding your proposed consumption rate, the proposed consumption is not supported by the data, and may significantly underestimate human exposures associated with use of the new product. Therefore, the information you provided regarding the addition of (b) (4) to the new product has not demonstrated that use of the new product would not result in exposures that exceed their respective human intake threshold of toxicological concern identified by the FAO/WHO Expert Committee on Food Additives (JEFCA) for these compounds. Even though these values have not been formally adopted by FDA as a standard for tobacco products, a consideration for the scientific basis of these reference values can inform the toxicological evaluation and are informative concerning whether the new products may raise different questions of public health. In addition, both (b) (4) are irritants, and thus prolonged exposures from use of smokeless tobacco products may contribute to local adverse effects on the buccal mucosa.

      Taken together, the data and justification you provided did not adequately demonstrate that the levels of these ingredients added to the new product are not of toxicological concern. The levels of (b) (4) may result in exposures that exceed their respective levels of toxicological concern identified by JEFCA. In addition, these ingredients are irritants, and thus prolonged exposures from use of smokeless tobacco products may contribute to local adverse effects on the buccal mucosa. Provide adequate scientific evidence (data, peer review articles, and/or other scientifically robust sources of information) to demonstrate that the addition of (b) (4) does not cause the new product to raise different question of public health.

4. SE0000487 and SE0000488 indicate that (b) (4) is present in the new products at levels higher than those found in corresponding surrogate predicate product (b) (4) is an HPHC; this compound is a strong skin irritant, and exposures may result in allergic contact dermatitis. For these reasons, additional information is needed (data, peer review articles, and/or other scientifically robust sources of information) to demonstrate that the levels of (b) (4) present in the new product do not cause the new product to raise different question of public health.

The Toxicology review considered the individual components that comprise complex ingredient (b) (4) Evaluation of this complex flavor is more appropriately addressed based on its individual components, as data informative to the toxicological evaluation is not available for the complex flavor but is available for its individual components. Note that, while additional details and method validation information is still needed to ensure validity of the HPHC data for all new tobacco products and the surrogate predicate product, an evaluation was completed under the assumption that the data is valid. For example, SE0000487 and SE0000488 indicate that the (b) (4) yield from the new tobacco products is increased compared to the surrogate predicate tobacco product. If the HPHC data were valid this would be of concern since (b) (4) is a carcinogen. Increases in HPHCs yields from the new products may consequently result in increased HPHC exposures for users of the new products compared to users of the predicate product. Also, of note, the use of a constant consumption rate for comparison of HPHC exposure estimates between users of the new and predicate products allows for determination of whether potential differences in HPHC exposures are due to differences in product characteristics.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a toxicology perspective.

4.5. SOCIAL SCIENCE

Social science reviews were completed by David Portnoy on October 10, 2013, Anh (Bao) Nguyen on December 23, 2014, and Elizabeth Donaldson on May 9, 2019.

The final social science review concludes that the new tobacco products have different characteristics compared to the predicate tobacco product and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health from a social science perspective. The final review identifies the following deficiencies that have *not* been adequately resolved:

1. All of your SE Reports provided information in response to the June 9, 2015 Preliminary Finding letter, however, your response to Deficiency #12 did not sufficiently address the flavor and format changes from the predicate product (C.C. Carhart's Choice) to the new products. The data you submitted comparing mint-flavored products to tobacco-flavored products did not include data on trial or initiation among non-users. Introducing the new mint flavor may increase product appeal among consumers compared to the predicate products and thus raise different questions of public health. Research suggests that enjoyment of flavor has been associated with initiation and continued use of smokeless tobacco products, particularly among youth and young adults (e.g., Ambrose et al. 2015; Smith et al., 2016; Villanti et al., 2017). The data you submitted regarding product format change did not include data on initiation of a product with the same format as the new product (i.e., dissolvable tobacco on a stick) and you did not include data on initiation of the predicate product and you did not bridge the data submitted to the new product. The studies you provided (e.g., Wolfson et al., 2014; Oliver et al. 2013) showed that flavor and format changes between the predicate product and the new products may raise different questions of public health. We need information on products with similar flavor and format changes to those proposed in your SE Reports in order to compare these products in a meaningful way. You could provide evidence or information on products that differ in flavor or format from the predicate and new products, but you should discuss why the information or evidence can be extrapolated to the predicate and new products. Furthermore, you should submit information and scientific evidence to demonstrate that the flavor and format changes between the new and predicate products do not cause the new products to raise different questions of public health, specifically questions regarding consumer perceptions, initiation among non-users, and increased use of the product. This information may include, but is not limited to:

    - Studies on new product and predicate product trial and initiation among non-tobacco users and former tobacco users;
    - Consumer perception studies comparing attitudes, beliefs, and behavioral intentions for the new product to the predicate product;
    - Market analyses (e g., sales and/or market segmentation analyses to identify likely consumers of the products); or
    - Other research and analyses conducted to prepare for introduction of the new products into the marketplace.

The applicant did not provide adequate evidence that the format changes between the predicate and new products do not raise different questions of public health from a Social Science perspective, specifically questions regarding consumer perceptions, initiation among non-users, and increased use of the product. Past research suggests that the dissolvable tobacco product format may be appealing due to perceptions of accessibility and convenience. Past research also suggests that dissolvable tobacco products may increase poly-tobacco use or decrease cessation, which also raise different questions of public health when compared to the format of the predicate product.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a social science perspective.

The review also evaluated the health information summary. The applicant originally submitted a health information summary which applied to all four SE reports. The first social science review noted that the health information summary potentially could cause a violation of section 911 of the FD&C Act. In response to the August 29, 2014 A/I letter, the applicant indicated that it would instead provide any health information related to the new tobacco products upon request by any party.

4.6. BEHAVIORAL AND CLINICAL PHARMACOLOGY

Behavioral and clinical pharmacology reviews were completed by Megan Schroeder on August 29, 2013, Lingling Guan on January 15, 2015, and Megan Schroeder on May 30, 2019.

The final behavioral and clinical pharmacology (BCP) review concludes that the new tobacco products have different characteristics related to consumer use of the product and impact on exposure and behavior compared to the predicate tobacco product and that the SE Reports lack adequate evidence to demonstrate that the differences with respect to addiction do not cause the new tobacco products to raise different questions of public health. The conclusions are based on:

1. Increased estimate of free nicotine in the new products compared to the predicate product.
2. Lack of actual product usage data needed to compare estimated HPHC exposure levels between users of the new and predicate products.
3. The addition of a characterizing flavor in some of the new products but not present in the predicate product.
4. Lack of data needed to compare nicotine release from the applicant's submitted nicotine dissolution studies.

However, as discussed in the Conclusion and Recommendation section of this TPL review, I conclude that the free nicotine content estimate does not sufficiently take into account the dissolution data and the analysis by the chemistry reviewer, and therefore such estimates of increases in free nicotine do not cause the new tobacco products to raise different questions of public health. In addition, I conclude that while the BCP raised relevant issues with regard to HPHC exposure levels, it did not account for toxicology considerations. Because exposure assessment evaluations of HPHCs is primarily a toxicology issue, the applicant's estimated HPHC exposure levels are properly evaluated by the toxicology reviewer. I also conclude that while the BCP raised relevant issues with regard to nicotine release, it did not account for the chemistry evaluation of the dissolution studies. Because dissolution is a chemical measurement, dissolution profiles are properly evaluated by the chemistry reviewer.

The review identifies the following deficiencies that have *not* been adequately resolved:

1. All of your SE Reports provide information on the amount of nicotine in the new products and predicate product. You claim that the new products have substantially less nicotine than the predicate product, and that topographical features are the primary driver of nicotine exposure in humans. You have provided estimations of product use behaviors for the new products and predicate products and claim that the differences in free nicotine in the new products do not raise different questions of public health. However, the studies used to estimate use of the new products and predicate product have several limitations. The study by Krautter and colleagues used Camel Sticks, and you have not adequately demonstrated that the data from Camel Sticks can be extrapolated to the new products in these SE Reports. In addition, Krautter et al., did not allow ad lib use of the study products so it is unknown how the products would be used in a more naturalized environment. The study by Winn et al., was performed in women diagnosed with oral or pharyngeal cancer, and the study subjects are not representative of the predominantly male smokeless tobacco user base. Finally, all of the studies used to estimate use of the new products were performed in smokers and you have not shown that smokers can provide an adequate estimation of dissolvable tobacco product use behaviors, and you have not demonstrated how use by smokers will show how the products will be used by ST users. It is unclear how the following differences in product characteristics affect product use behaviors and, consequently, nicotine bioavailability:

    - Free nicotine quantities
    - Portion sizes
    - Flavors
    - Format (e g., portioned and on a stick)

    Provide scientific evidence and rationale to demonstrate whether these differences result in different nicotine exposures from the new products and predicate product. A clinical study with quantitative plasma nicotine level assessments could be useful in determining whether the changed product characteristics result in different nicotine exposure rates and levels between the new and predicate products. There may be other ways to satisfy this deficiency, and you are responsible for identifying how best to do this.

TPL note for BCP Deficiency 1: This deficiency is based on an increased estimate of free nicotine in the new products compared to the predicate product. However, as discussed in the Conclusion and Recommendation section, the free nicotine content estimate does not sufficiently take into account the dissolution data and the analysis by the chemistry reviewer. Thus, this deficiency has been removed from the letter ready section of this review and will not be conveyed to the applicant.

2. All of Your SE Reports provide estimated HPHC exposure data for the new products and predicate products. You claim that the HPHC data and product usage data show that the potential exposure to HPHCs from the new products is significantly lower than the predicate product. However, as described above, the studies used to estimate use of the new products and predicate products have several limitations and may not accurately predict their use. Thus, the data are not adequate to address how the products will actually be used and whether the pre-portioned format of the new products will affect consumers' HPHC exposure levels. Provide actual product use data to support your assertion that the format differences (e.g., portioned and placed on a wooden dowel) in the new products do not raise different questions of public health. There may be other ways to satisfy this deficiency, and you are responsible for identifying how best to do this.

TPL note for BCP Deficiency 2: This deficiency is based on lack of product usage data, indicated by the BCP reviewer as necessary for the comparison of estimated HPHC exposure levels between users of the new and predicate products. However, as discussed in the Conclusion and Recommendation section, these concerns do not account for toxicology considerations. Thus, this deficiency has been removed from the letter ready section of this review and will not be conveyed to the applicant.

3. SE0000487 and SE0000533 provide information on the addition of a characterizing flavor to the new products compared to the predicate product, which does not contain a characterizing flavor. You state that you did not conduct research comparing the effects of the flavor differences between the new products and predicate products. You also claim that the literature on nicotine-containing products including moist smokeless tobacco products and nicotine gum does not support the conclusion that the addition of flavors to these products increases their abuse potential. However, the addition of characterizing flavors may cause the new products to raise different questions of public health due to changes in product attractiveness, tobacco addiction, and user behavior. In the absence of data examining the impact of flavorings on the use and abuse liability of the new products, we cannot assume that the new products have an equivalent abuse liability and will be used similarly to the predicate product. The provided scientific literature related to the potential impact of characterizing flavors on dependence does not address potential differences related to use behavior (e.g., amount and frequency of use, deposition time in the mouth, spitting) that may exist between the new and predicate products (see Deficiency 1). For example, Oliver et al . (2013) concluded that flavored smokeless tobacco products may influence initiation and maintenance of use; however, flavored products do not lead to greater product dependence. The generalizability of these findings is limited by its use of convenience sampling of smokeless tobacco users, some of whom were already seeking interventions to reduce or quit tobacco use. The data on the effect(s) of flavors on the use and abuse liability of nicotine gum may not be applicable to the new products and you have not demonstrated that nicotine gum is a suitable surrogate product or relevant to the new products. Provide adequate evidence that that addition of characterizing flavors to the new products does not cause the new products to raise different questions of public health. Such evidence could include a human abuse potential study or taste panel assessment to determine whether the differences in characterizing flavor cause the new products to raise different questions of public health. There may be other ways to satisfy this deficiency, and you are responsible for identifying how to best do this.

4. SE0000487, SE0000488, and SE0000533 provide data from an in vitro dissolution test. You claim that the nicotine content and estimated consumption rate of the new products are lower than those of the predicate products, that inexperienced smokeless tobacco users and youth are unlikely to use dissolvable tobacco products, and that the lower dissolution and nicotine content of the new products does not raise different questions of public health. However, you have not conducted any studies to determine whether the new products are appealing to novice and inexperienced tobacco users. Determination of substantial equivalence is based on comparison of a new tobacco product to a predicate tobacco product. The various survey-based studies (e g., McMillen et al., 2012; Wolfson et al., 2014; CDC, 2015) examining the use of a wide array of dissolvable tobacco products are not adequate for a determination of substantial equivalence to the predicate product. In addition, you did not provide the percentage nicotine released vs time. Without these data, we cannot compare the dissolution characteristics of the new and predicate products. In the absence of behavioral and pharmacokinetic data, it is unknown how the slower *nicotine release* will interact with the increased free nicotine *content* to affect nicotine exposure, initiation behaviors, tobacco addiction, and

> continued use. Provide adequate evidence that the differences in nicotine release do not cause the new products to raise different questions of public health. Such evidence could include a clinical pharmacokinetic study to determine actual nicotine exposure levels following use of the new and predicate products. There may be other ways to satisfy this deficiency, and you are responsible for identifying how to best do this.

TPL note for BCP Deficiency 4: The BCP review concludes that there was inadequate information to compare nicotine release from the applicant's submitted nicotine dissolution studies. However, as discussed in the Conclusion and Recommendation section, BCP's evaluation of nicotine release did not account for the chemistry analysis of the dissolution studies, which considered the applicant's studies sufficient to compare nicotine release between the new and predicate products. Therefore, this deficiency, as written in the May 30, 2019 BCP review, should not be conveyed to the applicant. The deficiency was revised to indicate that the dissolution characteristics of the new and predicate products could be compared and to reflect the conclusions of the chemistry review – that the new products release nicotine at slower rates than the predicate product.
The applicant also refers to the Summary TPSAC report on Dissolvable Tobacco Products, indicating the report states "*there is little use of [dissolvable tobacco products] by youth, even though several products have been on the market for about 10 years*." However, the report also states "*the TPSAC concluded that the available evidence, while limited, leads to a qualitative judgment that availability of DTPs could increase the number of users of tobacco products. This judgment was based on experience with other STs, data presented from the State of Indiana showing that some adolescents were already using DTPs, the survey data on youth perceptions of the products from the State of Virginia, and the potential for youth to be drawn to a novel product*." Therefore, this information did not demonstrate that the slower release of nicotine in the new products compared to the predicate product do not make the new products more appealing to youth and inexperienced smokeless tobacco users, and thus do not cause the new products to raise different questions of public health.

The following revised deficiency will be included (replacing BCP Deficiency 4) in the letter ready section of this review and conveyed to the applicant:

> All of your SE Reports provide dissolution data measuring total nicotine in artificial saliva fractions collected using a USP-4 flow-through dissolution apparatus. The dissolution data demonstrate that the new products release nicotine at slower rates than the predicate product. The slower release of nicotine may make the new products less aversive than the predicate product and more appealing to youth and inexperienced smokeless tobacco users. You indicate that you have not conducted studies to assess whether the new products are appealing to inexperienced users as the new products are intended for current adult tobacco product users and provide published literature on the likelihood of use and reported actual use of dissolvable tobacco products among adults. You claim that these survey-based studies (e.g., McMillen et al., 2012; Romito & Saxton, 2014; Wolfson et al., 2014) show the use of dissolvable tobacco products among adults is low, largely confined to users of other tobacco products, and that likelihood of trial by non-users of tobacco products was low. You also indicate that results from the CDC National Youth Tobacco Survey demonstrate that use of dissolvable tobacco products has been consistently low in youth populations, and that these available survey data do not support literature suggesting dissolvable tobacco products may appeal to youth. However, the provided studies examined the use of a wide array of dissolvable tobacco products, and no data was provided on the characteristics of the dissolvable tobacco products in these studies (e.g., Camel Sticks) to explain how that information could be bridged to the new products. Therefore, you did not demonstrate that the characteristics of the products in these studies are comparable to the new products and that these data can be bridged to the new products that are the subject of these SE Reports. You also refer to the Summary TPSAC report on Dissolvable Tobacco Products, indicating the report states "*there is little use of [dissolvable tobacco products] by youth, even though several products have been on the market for about 10 years*." However, the report also states "*the TPSAC concluded that the available evidence, while limited, leads to a qualitative judgment that availability of DTPs could increase the number of users of tobacco products. This judgment was based on experience with other STs, data presented from the State of Indiana showing that some adolescents were already using DTPs, the survey data on youth perceptions of the products from the State of Virginia, and the potential for youth to be drawn to a novel product*." The information you provided did not demonstrate that the slower release of nicotine in the new products compared to the predicate product do not make the new products more appealing to youth and inexperienced smokeless tobacco users, and thus do not cause the new products to raise different questions of public health. You needed to provide sufficient scientific evidence and rationale that the differences in nicotine release do not cause the new products to raise different questions of public health. Such evidence could have included information on use behaviors for the new and predicate products. There may be other ways to satisfy this deficiency, and you are responsible for identifying how to best do this.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a behavioral and clinical pharmacology perspective.

4.7. MEDICAL

Medical reviews were completed by Priscilla Callahan-Lyon on August 8, 2013, and December 24, 2014.

The final medical review concludes that the new tobacco products have different characteristics from the predicate tobacco product but the differences do not cause the new tobacco products to raise different questions of public health from a medical perspective. The review identifies the following differences:

1. Physical injuries related to product usage patterns and product design
2. Inadvertent nicotine exposure, especially for small children

The applicant submitted a hazard analysis of the new tobacco products for the differences listed above, to demonstrate that the new tobacco products have a low potential of creating these hazards. The potential hazards associated with the new tobacco products could be physical (e.g., mouth cuts) or pharmacological (e.g., nicotine poisoning). The primary potential physical hazards identified were related to possible cut injuries or oral ingestion injuries associated with having a small piece of wood in the mouth or having such material left on the ground. Due to the similarities of size and shape, injures explored were those reported for toothpicks. Annual injury rates associated with toothpicks are quite low with majority of reported events resulting in persons being treated and released or requiring no treatment. In addition, the blunted ends of the wooden dowel in the new tobacco products lessens the chances of physical injury. Thus, the reviewer agrees with the applicant's conclusion that the likelihood of significant injury from the wooden dowel is low.

The applicant also submitted an analysis on nicotine toxicity and potential risks of accidental exposure to the new tobacco products – particularly for children and noted that the likelihood of significant nicotine exposure is low, as the quantity of nicotine on a single tobacco stick is no more than 2.25 mg. The reviewer agrees with this conclusion. Even a small child (< 10 kg) would need to ingest the

entire contents of more than one tobacco stick to absorb a quantity of nicotine likely to cause an adverse effect. Therefore, the differences in product characteristics between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a medical perspective.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order finding a tobacco product not substantially equivalent (NSE) under section 910(a) of the FD&C Act is categorically excluded and, therefore, normally does not require the preparation of an environmental assessment (EA) or environmental impact statement. FDA has considered whether there are extraordinary circumstances that would require the preparation of an EA and has determined that none exist.

6. CONCLUSION AND RECOMMENDATION

The following are the key differences in characteristics between the new tobacco products and the predicate tobacco product:

- Fundamental product design differences: portioned, dried tobacco slurry held together by binders on a wooden dowel (stick) versus non-portioned, loose dry snuff
- Addition of characterizing flavor[3]Addition of ingredients (e.g., (b) (4) [4]
- Increased acetaldehyde and (b) (4) yields[5]
- Increase in permeation enhancers (e.g. (b) (4))[6]
- Decreased total nicotine release rate
- Estimated increased free nicotine quantity

The applicant has failed to demonstrate that some of these differences in characteristics do not cause the new tobacco products to raise different questions of public health. Of note, the applicant is using a loose dry snuff tobacco product as a predicate product whereas the new tobacco products are sticks, a type of smokeless tobacco product. These two sub-classes of smokeless products have unique characteristics (portioned versus non-portioned; ingested versus non-ingested; and dried tobacco slurry with binders versus loose dry snuff, for the new versus predicate products, respectively) when compared to each other and the applicant has failed to demonstrate that these difference in characteristics do not cause the new products to raise different questions of public health.. Therefore, the applicant has failed to provide sufficient information to support a finding of substantial equivalence.

The predicate tobacco product meets statutory requirements because it was determined that it is a grandfathered product (i.e., was commercially marketed in the United States other than exclusively in test markets as of February 15, 2007).

The chemistry, engineering, toxicology, social science, and behavioral and clinical pharmacology (BCP) reviews conclude that the new tobacco products have different characteristics compared to the predicate tobacco product and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. Overall, I concur with most of the comments contained in these reviews and recommend that NSE order letters be issued. However, upon review of the administrative record, as TPL I found that there was relevant information that was not adequately assessed. Specifically, BCP concerns related to increased free nicotine content estimate does not sufficiently take into account the dissolution data and the analysis by the chemistry reviewer. Also, while BCP raised relevant issues with regard to nicotine release, it did not account for the chemistry evaluation of the dissolution studies. Further, estimated daily exposure to HPHCs from use of the new and surrogate predicate tobacco products was evaluated by the BCP reviewer in addition to the Toxicology reviewer, and the BCP reviewer drew conclusions that were contradictory to the typical practice of the Toxicology review standard. The identified issues are discussed further below.

<u>Free nicotine measurement:</u>
The applicant provided dissolution data measuring total nicotine in artificial saliva fractions collected using USP-4 flow-through dissolution apparatus in their response to FDA's August 2014 Advice/Information Request letter. The BCP reviewer found that the dissolution studies did not address the concern of increased free nicotine in the new tobacco products.

My scientific determination is that the dissolution data submitted by the applicant are sufficient to address concerns raised regarding increases in free nicotine in the new products. I base this opinion on the following evidence: 1) flaws in the weight placed on calculated free nicotine; and 2) the dissolution results and the chemist's evaluation of those results. Each of these pieces of evidence are discussed more fully below:

1. The BCP reviewer states that, *". . . the calculated percent free nicotine is higher in the new products compared to the predicate products due to the increased pH of the new products."* This statement is based solely upon the Henderson-Hasselbach Equation (HHE), which is a method for approximating the free nicotine content in a solution. The HHE equation calculates the amount of free nicotine based solely upon the solution pH and the knowledge of the dissociation constant of nicotine. The HHE calculates the amount of free nicotine present when a solution is at equilibrium, but it does not consider important confounding effects such as dynamic salivary flow, tobacco cut size, fillers and other ingredients, or the effect of transport across the oral mucosa upon the equilibrium condition. Thus, the HHE is best used as tool for the approximation of the maximum amount of free nicotine that could be present rather than an indication that all of this free nicotine is available immediately. A finding of a significant change in the free nicotine based on an HHE evaluation should be used as a *signal* that a more representative approach to estimating free nicotine is needed.

2. Here, the applicant supplied a more representative approach by submitting the results of dissolution testing. Dissolution testing measures the nicotine release in a condition that more closely resembles the human equivalent and accounts for most of the confounding differences that the HHE cannot. The results of a dissolution study provide a measure of the total nicotine released over a period of time. This specific dissolution test constantly exposes the tobacco product with fresh media in small volume increments, which better represents the conditions of use than HHE. The 2nd cycle Chemistry review of the dissolution data concluded that the new products release nicotine at much slower rates than the predicate product. Thus, the dissolution data does not support the free nicotine levels estimated by reviewers using the HHE. This is likely due, in part, to the addition of (b) (4) ingredients in the new products that are not accounted for in the HHE. The applicant states that the (b) (4)

[3] SE0000487 and SE0000533 only.
[4] SE0000547 only.
[5] (b) (4) increases in SE0000547 only; (b) (4) increases in SE0000487 and SE0000488 only.
[6] SE0000487 and SE0000533 only.

(b) (4) *in the new products serve to hold the tobacco matrix together and the data suggest that, consequently, these* (b) (4) *may impede constituents release.*" While the dissolution data is a measure of the total nicotine instead of free nicotine, only nicotine in solution will dissociate to free nicotine. As described in the HHE, the nicotine to free nicotine ratio is fixed by the pH of the immediate solution; thus, the amount of free nicotine available at any given point in time is directly related to the total nicotine content. Therefore, dissolution provides the best in vitro means to predict free nicotine release rates. However, these data will only provide an estimate of free nicotine and only through pharmacokinetic or pharmacodynamic measurements can free nicotine transport be definitively evaluated.

In summary, I disagree with the BCP reviewer's conclusion that human pharmacokinetic data are necessary to evaluate differences in nicotine exposure rates and levels between the new and predicate products. The BCP reviewer based that determination on the evaluation of the change in calculated free nicotine between the new and predicate tobacco products. However, this difference was calculated using the HHE, which can provide an inflated measurement of total free nicotine content. Instead, the dissolution profiles provide a better estimate of free nicotine release rates and content than the HHE. I find that the applicant's dissolution data and the analysis by the chemistry reviewer combined are sufficient evidence to demonstrate that there is not a significant increase in free nicotine in the new tobacco products. Therefore, the deficiency identified in the BCP review regarding the free nicotine differences between the new and predicate products, should not be conveyed to the applicant, because I conclude that the apparent free nicotine increases are not supported by the data provided.

Nicotine dissolution rate:
The applicant provided dissolution data measuring total nicotine in artificial saliva fractions collected using a USP-4 flow-through dissolution apparatus in their response to FDA's August 2014 Advice/Information Request letter. The BCP reviewer states that the dissolution characteristics of the new and predicate products cannot be compared, while also indicating it is not reasonable to assume that the nicotine release rates of the new products are slower than the predicate product in vivo based on the dissolution studies.

I conclude that while the BCP raised relevant issues regarding nicotine release (e g., product appeal), it did not account for the chemistry evaluation of the dissolution studies. Because dissolution is a chemical measurement, dissolution profiles are properly evaluated by the chemistry reviewer. The 2nd cycle Chemistry review states "*. . . we can conclude that the new products release nicotine at much slower rates than the predicate product . . .We refer to addiction review for an evaluation on the potential implication of significant differences in nicotine release rate between the new and predicate products*." Therefore, the deficiency identified in the BCP review regarding dissolution studies should be edited to indicate that the dissolution characteristics of the new and predicate products could be compared and that the new products release nicotine at slower rates than the predicate product. Concerns about the impact of slower nicotine release on product appeal to youth and inexperienced smokeless tobacco users should be conveyed to the applicant.

Also, of note, the BCP deficiency only indicates that the dissolution studies are relevant to three of the four new products. However, the 2nd cycle Chemistry review indicates the dissolution studies are relevant to all SE Reports, stating *"[t]he applicant stated that they did not perform dissolution studies with the new product for SE0000547 because the flavor profile is very similar to the new product for SE0000488. This explanation is acceptable because the results showed that nicotine and TSNA releases are similar among the 3 new products tested and independent of the flavor system. Therefore, we expect that the release profiles for nicotine and TSNAs for the new product for SE0000547 (the one that was not tested) would show similar patterns to the 3 new products tested by the applicant.*" Thus, the deficiency conveyed to the applicant should indicate that concerns apply to the new tobacco products in all SE Reports.

HPHC exposures:
The applicant proposed consumption rates for the new and predicate products to evaluate users' potential daily exposure to HPHCs. The BCP reviewer states that without actual use data for the new and predicate products, HPHC exposures are unknown.

I conclude that while the BCP raised relevant issues with regard to HPHC exposure levels, it did not account for toxicology considerations. Because exposure assessment evaluations of HPHCs is primarily a toxicology issue, the applicant's estimated HPHC exposure levels are properly evaluated by the toxicology reviewer. The Toxicology review indicates the mean daily use of conventional smokeless tobacco products reported in published literature ranges between (b) (4) (Hecht et al., 2008) and (b) (4) (Hecht et al., 2007) with a central value of (b) (4) based on the use patterns evaluated by Hatsukami et al. (1988). For the predicate product, the applicant proposes a reasonable consumption rate of (b) (4) consistent with the central value of (b) (4) for conventional smokeless tobacco products from published literature. The exact tobacco consumption levels for the new products cannot be established based on the applicant's internal studies or data available in the published literature. However, in the absence of data specific for these new products, Toxicology considers the mean daily use of total tobacco to be equivalent to that from the predicate product. The use of a constant consumption rate for comparison of HPHC exposure estimates between users of the new and predicate products allows for determination of whether potential differences in HPHC exposures are due to differences in product characteristics. Exposure estimates generated using different consumption rates for new and predicate products are influenced by both differences in product characteristics and use behaviors. Therefore, in the absence of data demonstrating differences in consumption rates between users of the new and predicate products, a constant consumption rate for new and predicate products is employed by Toxicology for exposure assessment evaluations in the context of SE review. Also noting, the product user population is assumed to be the same for the new and predicate product in SE evaluations, where the intent is to identify potential relative differences in HPHC exposures (and thus user risk) for users of the new product compared to those of the predicate product. Therefore, the deficiency identified in the BCP review regarding the need for actual use data to estimate HPHC exposures should not be conveyed to the applicant, as this was evaluated in the Toxicology review.

Because the proposed action is issuing NSE orders, it is a class of action that is categorically excluded under 21 CFR 25 35(b). FDA has considered whether there are extraordinary circumstances that would require the preparation of an environmental assessment and has determined that none exist. Therefore, the proposed action does not require preparation of an environmental assessment or an environmental impact statement.

NSE order letters should be issued for the new tobacco products in SE0000487, SE0000488, SE0000533, and SE0000547, as identified on the cover page of this review.

1. All of your SE Reports include harmful and potentially harmful constituent (HPHC) testing results but does not specify the number of replicates, standard deviations, or the validation parameters of the procedures. It is also unclear how HPHC measurements identified as BLOQ were considered in your calculations of estimated daily exposure to HPHCs from use of the new and surrogate predicate tobacco products (calculated daily exposure estimates presented in Table 2 of your July 2015 amendment). For example, did you consider daily exposure to HPHCs reported as Below Limit of Quantification (BLOQ) to be zero or was the limit of quantification value used in the absence of a measured value? Without this information, a full evaluation of the HPHC data was not possible.

2. All of your SE Reports includes HPHC testing results, but additional information was needed on the analytical methods in order to fully evaluate the HPHC data. Each of the analytical methods lacks sufficient detail and validation data. For example, you reported data below the limit of quantification but did not provide the limit of quantification. To adequately review your SE Report, the following information for AM-187, SOP-210, AM-052, and AM-189 would be needed:

    a. Complete description of the instrumentation used;
    b. Step-by-step instructions for the sample preparation, standard preparation, and calibration curves solutions;
    c. Instrument settings such as split ratio, carrier gas, injection volume, injection type, injector temperature, temperature gradient, column type and dimensions, and detector settings;
    d. Validation information, including precision, accuracy, specificity, limit of quantification, and limit of detection; and
    e. Demonstration that the analytical methods are suitable to report the results provided in Table 1 of your July 2015 amendment.

    In addition, the following clarifications would be needed for the specified methods:

    f. Filler Metals (AM-052) includes a description of an ICP-MS measurement of digested tobacco samples. In the description, the procedure states that "cut filler" is digested and measured. However, the new and surrogate predicate tobacco products are defined as milled tobacco. The description does not indicate the manner in which the new product was sampled. In addition, the description does not address the potential for the inclusion of additional metals from the environment, unintentional contamination, or product contact with metal surfaces from the milling process used to generate the final milled form of the new products. It is also unclear which products were tested.

3. While additional details and method validation information is still needed to ensure validity of the HPHC data, an evaluation was completed under the assumption that the data is valid. The submitted data indicate that the following HPHCs are present at higher levels in the new products compared to the surrogate predicate product:

    - SE0000487: (b) (4)
    - SE0000488: (b) (4)
    - SE0000547: (b) (4)

    (b) (4) are carcinogens. (b) (4) is also is a strong skin irritant, and exposures may result in allergic contact dermatitis. Increases in HPHCs yields from the new products may consequently result in increased HPHC exposures for users of the new products compared to users of the predicate product. For these reasons, additional information (data, peer review articles, and/or other scientifically robust sources of information) to demonstrate that the levels of HPHCs present in the new products do not cause the new products to raise different question of public health was needed.

4. All of Your SE Reports states that the Filler Metals (AM-052) analysis was performed by Enthalpy Laboratory (previously Arista Laboratories), which is ISO 17025 accredited and is specifically accredited to perform the procedure to measure (b) (4) and (b) (4) However, your SE Reports do not provide the accreditation for the following methods:

    a. B[a]P (AM187)
    b. Carbonyls (AM189)
    c. TSNA (SOP210)

    Clarification on the accreditation status for these specific procedures was needed to understand the capability of the laboratory used to measure these HPHCs.

5. All of your SE Reports provided a response to Deficiencies 1 and 14 in your July 2015 amendment which included an appendix in which the analytical procedures used to measure HPHCs in the new products and a surrogate predicate product are briefly described. In the description titled "Smokeless Tobacco TSNA – SOP-210", you state that the "Pouched products are weighed…"and extracted, and the extracted samples are analyzed by GC-MS/MS for nitrosamines (NNN and NNK). Thus, it appears that the TSNA testing with method SOP-210 was conducted for unknown pouched tobacco products with unknown product characteristics and was not conducted on the specific new (sticks) and surrogate predicate (dry snuff) products submitted for evaluation in these SE Reports. The comparisons conducted in SE reviews evaluate differences between specific new and predicate products; they are not evaluations between the new products and other marketed tobacco products that are neither the new product nor the [surrogate] predicate product. In addition, the methodology provided for SOP-210 differs from the methodology provided in your response to Deficiency 4, where you outline two other procedures that you used to measure NNN and NNK. In your Deficiency 4 response, you state that different methods were used for the measurement of TSNAs in the new and predicate products. For the new products, you indicate that TSNA testing with an ALCS method that followed CORESTA Recommended Method (CRM) No. 72 and No. 75 was conducted, where samples were analyzed by LC-MS/MS for NNN and NNK. For the predicate product, you indicate that TSNA testing with a USSTC method that followed ISO/TS 22304 and CRM No. 63 was conducted, where samples were analyzed by GC-TEA for NNN and NNK. You state that the two procedures have been used as part of a 2009 CORESTA collaborative study and that the variance measurements for both procedures were in an acceptable range and thus the methods were comparable. The inclusion of procedures in a collaborative study does not necessarily indicate that the procedures are comparable. In order to compare the results of the TSNA studies for the new and predicate products, results of comparisons using the same procedure or the complete method comparison study using common measurements with a predetermined level of variability that is linked to the acceptance criteria for the TSNA measurements was needed. Alternatively, you could have explained why the methods are comparable. In addition, it is unclear if the predicate product or the surrogate predicate product was used for TSNA testing. In your responses to Deficiencies 1 and 14 you indicate the surrogate predicate product is used for TSNA level comparisons with the new products, however, in your response to Deficiency 4 you indicate the predicate product is used. Clarification on whether the predicate product or the surrogate predicate product was used for TSNA testing was needed.

6. All Your SE Reports fail to show that the differences in design characteristics between the new and predicate products (portioned versus non-portioned; ingested versus non-ingested; and dried tobacco slurry held together by binders versus loose dry snuff, respectively) do not cause the new products to raise different questions of public health in comparison to the predicate product. The information provided about these design differences is insufficient to demonstrate that it is appropriate and valid to perform a comparison of substantial equivalence between these product categories. The new products have the following design parameters:

    a. Tobacco particle size;
    b. Final moisture;

c. Final portion weight;
d. Tobacco coating length;
e. Tobacco coating width;
f. Tobacco coating thickness;
g. Tobacco coating weight;
h. Dowel weight;
i. Dowel length;
j. Dowel width and taper; and
k. Finishing agents used on the dowel.

In contrast, the predicate product has the following design parameters:

l. Tobacco particle size; and
m. Final moisture.

You did not provide a scientific discussion and rationale as to why these dissimilarities in the design characteristics of new and corresponding predicate products do not cause the new products to raise different questions of public health. You needed to address each of the design characteristics listed above and provide adequate scientific evidence and rationale to demonstrate that these fundamental design characteristic differences do not cause the new products to raise different questions of public health.

7. SE0000487, SE0000488, SE0000533 and SE0000547 contained information on the consumption rate of the new products compared to the predicate tobacco products. Product consumption rates, combined with substance concentration data are essential aspects of the exposure assessment used to evaluate the potential toxicological impacts from consumer exposures to ingredients and other constituents (e g., HPHCs) in the products under consideration. For SE0000487, SE0000488, SE0000533 and SE0000547, you assert that (b) sticks/day (approximately (b) (4) tobacco/day) represents "*the 90th percentile consumption*" which indicates that 90% of the users of the new products consume approximately (b) (4) tobacco/day, or less; and for the predicate product you provide a mean tobacco consumption rate (b) (4) tobacco/day. The data and justification you provided do not support the proposed tobacco consumption rate of approximately (b) (4) tobacco/day for users of your new products:

   a. The proposed consumption rate was calculated using data from the (b) (4) (b) (4) .

   b. You provided the study by Krautter et al. (2015) as supportive evidence for the proposed consumption rate. However, this study does not provide adequate evidence for the following reasons:

      i. The study by Krautter et al. (2015) did not allow the study participants to use tobacco sticks *ad libitum*. Due to the restrictions on product use, the tobacco stick consumption data from this study may have underestimated the true consumption rate in a population of smokeless tobacco users that use the product *ad libitum.*
      ii. Even with the restriction placed by Krautter et al. (2015) on the number of tobacco sticks study subjects were allowed to use in a day, the study reported a use rate for the tobacco sticks (mean±SD) of 6.39±4.44 sticks/day, which is higher than the consumption rate of (b) sticks/ day you proposed as the 90th percentile consumption rate. Moreover, the tobacco sticks used by Krautter et al. (2015) contained 486 mg of tobacco per stick, which results in a mean tobacco use rate of approximately 3.1 grams tobacco/day (6.39 sticks/day X 486 mg of tobacco per stick), further suggesting that the proposed consumption rate of (b) sticks/day (approximately (b) (4) tobacco/day) significantly underestimates the total amount of tobacco that would be consumed by users of the new products.
      iii. Krautter et al. (2015) also showed that total nicotine exposure for the study subjects was consistent across users of all the tobacco products evaluated (i.e., dual use, snus, sticks, strips and orbs). Based on this study, users of the new products would consume the amount of tobacco that would result in nicotine intake levels equivalent to the nicotine intake from the predicate product. The proposed consumption rate of (b) sticks/day (b) (4) tobacco/day) would result in exposure to nicotine from use of your new product that is less than the nicotine exposure from the predicate product; you provided a mean consumption rate (b) (4) tobacco/day for the predicate product. Thus, the finding of equivalent nicotine intake in the study by Krautter et al. (2015) suggests a significantly higher usage than (b) sticks/day.

   c. To support the consumption rate o (b) sticks/day for your new products, you assume that a consumer uses one tobacco stick in 15 minutes and conclude that "consumption rates higher than those reported in the extended use study are not reasonable given what is currently known about smokeless tobacco topography". Your conclusion is not supported by the information and data you provided:

      i. (b) (4)
      ii. You also provided the following information and assumptions that are relevant to estimating the number of tobacco sticks that could be consumed per day, based on what is currently known about smokeless tobacco topography:
         - The consumption time per stick can be estimated from 1) the cigarette use time of 10 min, and 2) the information from study participants indicating that consumption time per stick is lower than consumption per cigarette. Therefore, the consumption time per stick is <10 minutes; >6 sticks can therefore be consumed per hour of smokeless tobacco use.
         - You estimated a total smokeless tobacco use time of 4.2 hours per day based on the study by Hatsukami et al., (1988). Therefore, the information provided on the characteristics and duration of use for the tobacco

sticks, indicates that users of the new products may consume >24 tobacco sticks/day (>6 sticks/hour of tobacco use x 4.2 hours of tobacco use/day).

Taken together, the proposed (90th percentile) consumption rate of (b) sticks/day is not supported by the data, published literature and justifications you provided. Notably, the study you cited (i(b) (4)) indicates that (b) (4) . Published literature for mean consumption rates of other smokeless tobacco products shows a daily tobacco use range between 5.3 and 20.4 g/day (central published value of 12 g/day), which is equivalent to approximately 23 - 89 sticks of the new products per day (with a central value of 52)). Another study you cited (Hatsukami et al., [1988]) estimates a total smokeless tobacco use time of 4.2 hours per day, and additional information you provided indicates that users of the new products may be able to consume >6 sticks/hour of tobacco use. This indicates that users of the new products may consume >24 tobacco sticks/day. The data and justification you provided did not adequately demonstrate a lower tobacco use rate for the new product as compared to the corresponding predicate product. In the absence of data demonstrating a lower tobacco use rate for the new products as compared to the corresponding predicate products, the toxicological evaluation of differences between the new and predicate products in these SE Reports, the daily tobacco use for the new product is assumed to be the same as that for the corresponding predicate product. The use of a constant consumption rate for comparison of HPHC exposure estimates between users of the new and predicate products allows for determination of whether potential differences in HPHC exposures are due to differences in product characteristics. You needed to provide adequate scientific evidence and rationale to demonstrate consumption rates of the new and predicate products, including published literature for smokeless tobacco sticks.

8. SE0000487 and SE0000533 provide justification regarding the addition of permeation enhancers (b) (4) in SE0000487 and SE0000533; (b) (4) in SE0000533) to the new products, but the submitted information does not demonstrate that the levels of these ingredients would not increase buccal permeability and uptake of HPHCs. (b) (4)

(b) (4)

(b) (4) The effect of permeation enhancers such as (b) (4) on the uptake of compounds via the buccal mucosa depends on the concentrations and physicochemical properties of the compounds. Chemical permeation enhancers can increase uptake of compounds via the buccal mucosa by various mechanisms, and within short exposure durations. You needed to provide evidence that this is not a concern and does not cause the new products to raise different questions of public health.

9. SE000547 indicates that (b) (4) (CAS (b) (4)), (b) (4) (CAS (b) (4)) and (b) (4) (CAS (b) (4)) are added to the new product but are not present in the predicate product, the information you provided did not adequately address the concerns for these ingredients:

   a. (b) (4) (CAS (b) (4)): You assert that the (b) (4) cut-off value used to classify Structure Category A food additives as Concern Level I (FDA, May 18, 2014) is an appropriate comparator value to evaluate exposures to this ingredient from the new product. The "Concern Level" classifications in this guidance document (Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Foods) are used to identify the corresponding recommendations for toxicity testing; these do not provide information on levels of oral exposures below which adverse effects are not likely to occur. For example, for compounds identified as Concern Level I (cut-off values of (b) (4) for Structure Category A additives), the referenced Guidance recommends genetic toxicity tests and short-term toxicity tests with rodents. Since these classification criteria do not provide toxicity-based reference levels protective for human oral exposures, the (b) (4) cut-off limit is not considered an appropriate comparator value to evaluate potential toxicity from human exposures to (b) (4) from tobacco product use. This review considered the individual components that comprise complex ingredient (b) (4) Evaluation of this complex flavor is more appropriately addressed based on its individual components, as data informative to the toxicological evaluation is not available for the complex flavor but is available for its individual components.

      (b) (4) contains (b) (4) CAS (b) (4) . As discussed in detail above regarding your proposed consumption rate, the consumption rate o (b) sticks/day for your new products is not supported by the data and may significantly underestimate exposures from use of the new product. For smokeless tobacco, published literature supports a mean consumption rates of 5.3-20.4 g/day of tobacco (central published value of 12 g/day), which are equivalent to approximately 23 –89 sticks per day (with a central value of 52). The level of (b) (4) in the new product from the (b) (4) may result in exposure levels that exceed the possible average daily intake (PADI) estimated by the Flavor and Extract Manufactures Association (FEMA) for flavors in foods, and the FAO/WHO Expert Committee on Food Additives (JEFCA) human intake threshold of concern for this compound. Even though these values have not been formally adopted by FDA as a standard for tobacco products, a consideration for the scientific basis of these reference values can inform the toxicological evaluation and are informative concerning whether the new products may raise different questions of public health. In addition, (b) (4)] is an irritant and sensitizer, which are relevant effects for the oral mucosa given that the new products are smokeless tobacco products.

   b. (b) (4) (CAS (b) (4))-and (b) (4) (CAS (b) (4)): In response to these concerns for these ingredients you provided exposure estimates to these compounds from product use that were calculated using the proposed consumption rate of (b) sticks/day. As discussed in detail above regarding your proposed consumption rate, the proposed consumption is not supported by the data, and may significantly underestimate human exposures associated with use of the new product. Therefore, the information you provided regarding the addition of (b) (4) to the new product has not demonstrated that use of the new product would not result in exposures that exceed their respective human intake threshold of toxicological concern identified by the FAO/WHO Expert Committee on Food Additives (JEFCA) for these compounds. Even though these values have not been formally adopted by FDA as a standard for tobacco products, a consideration for the scientific basis of these reference values can inform the toxicological evaluation and are informative concerning whether the new products

may raise different questions of public health. In addition, both (b) (4) and (b) (4) are irritants, and thus prolonged exposures from use of smokeless tobacco products may contribute to local adverse effects on the buccal mucosa.

Taken together, the data and justification you provided did not adequately demonstrate that the levels of these ingredients added to the new product are not of toxicological concern. The levels of (b) (4) (as a component of (b) (4)) (b) (4) (b) (4) and (b) (4) may result in exposures that exceed their respective levels of toxicological concern identified by JEFCA. In addition, these ingredients are irritants, and thus prolonged exposures from use of smokeless tobacco products may contribute to local adverse effects on the buccal mucosa. You needed to provide adequate scientific evidence (data, peer review articles, and/or other scientifically robust sources of information) to demonstrate that the addition of (b) (4) (as a component of (b) (4) (b) (4) and (b) (4) does not cause the new product to raise different question of public health.

10. All of your SE Reports provided information in response to the June 9, 2015 Preliminary Finding letter, however, your response to Deficiency #12 did not sufficiently address the flavor and format changes from the predicate product (C.C. Carhart's Choice) to the new products. The data you submitted comparing mint-flavored products to tobacco-flavored products did not include data on trial or initiation among non-users. Introducing the new mint flavor may increase product appeal among consumers compared to the predicate products and thus raise different questions of public health. Research suggests that enjoyment of flavor has been associated with initiation and continued use of smokeless tobacco products, particularly among youth and young adults (e.g., Ambrose et al. 2015; Smith et al., 2016; Villanti et al., 2017). Research also suggests that dissolvable tobacco product format may be appealing due to perceptions of accessibility and convenience, and that dissolvable tobacco products may increase poly-tobacco use or decrease cessation. The data you submitted regarding product format change did not include data on initiation of a product with the same format as the new product (i.e., dissolvable tobacco on a stick) and you did not bridge the data submitted to the new product. The studies you provided (e.g., Wolfson et al., 2014; Oliver et al. 2013) showed that flavor and format changes between the predicate product and the new products may raise different questions of public health. We needed information on products with similar flavor and format changes to those proposed in your SE Reports in order to compare these products in a meaningful way. You could have provided evidence or information on products that differ in flavor or format from the predicate and new products, but you should have discussed why the information or evidence can be extrapolated to the predicate and new products. Furthermore, you may have submitted information and scientific evidence to demonstrate that the flavor and format changes between the new and predicate products do not cause the new products to raise different questions of public health, specifically addressing questions regarding consumer perceptions, initiation among non-users, and increased use of the product. This information may include, but is not limited to:

    - Studies on new product and predicate product trial and initiation among non-tobacco users and former tobacco users;
    - Consumer perception studies comparing attitudes, beliefs, and behavioral intentions for the new product to the predicate product;
    - Market analyses (e.g., sales and/or market segmentation analyses to identify likely consumers of the products); or
    - Other research and analyses conducted to prepare for introduction of the new products into the marketplace.

11. SE0000487 and SE0000533 provide information on the addition of a characterizing flavor to the new products compared to the predicate product, which does not contain a characterizing flavor. You state that you did not conduct research comparing the effects of the flavor differences between the new product and predicate product. You also claim that the literature on nicotine-containing products including moist smokeless tobacco products and nicotine gum does not support the conclusion that the addition of flavors to these products increases their abuse potential. However, the addition of characterizing flavor may cause the new product to raise different questions of public health due to changes in product attractiveness, tobacco addiction, and user behavior. In the absence of data examining the impact of flavorings on the use and abuse liability of the new products, we cannot assume that the new product has an equivalent abuse liability and will be used similarly to the predicate product. The provided scientific literature related to the potential impact of characterizing flavors on dependence does not address potential differences related to use behavior (e.g., amount and frequency of use, deposition time in the mouth, spitting) that may exist between the new and predicate product. For example, Oliver et al., 2013 concluded that flavored smokeless tobacco products may influence initiation and maintenance of use; however, flavored products do not lead to greater product dependence. The generalizability of these findings is limited by its use of convenience sampling of smokeless tobacco users, some of whom were already seeking interventions to reduce or quit tobacco use. The data on the effect(s) of flavors on the use and abuse liability of nicotine gum may not be applicable to the new product and you have not demonstrated that nicotine gum is a suitable surrogate product or relevant to the new product. You needed to provide adequate evidence that that addition of a characterizing flavor to the new products does not cause the new products to raise different questions of public health. Although it is up to the applicant to decide what approach would be appropriate to provide the evidence, some approaches to provide such evidence could have included, for example, a human abuse potential study or taste panel assessment to determine whether the differences in characterizing flavor cause the new products to raise different questions of public health.

12. All of your SE Reports provide dissolution data measuring total nicotine (b) (4) . The dissolution data demonstrate that the new products release nicotine at slower rates than the predicate product. The slower release of nicotine may make the new products less aversive than the predicate product and more appealing to youth and inexperienced smokeless tobacco users. You indicate that you have not conducted studies to assess whether the new products are appealing to inexperienced users as the new products are intended for current adult tobacco product users and provide published literature on the likelihood of use and reported actual use of dissolvable tobacco products among adults. You claim that these survey-based studies (e.g., McMillen et al., 2012; Romito & Saxton, 2014; Wolfson et al., 2014) show the use of dissolvable tobacco products among adults is low, largely confined to users of other tobacco products, and that likelihood of trial by non-users of tobacco products was low. You also indicate that results from the CDC National Youth Tobacco Survey demonstrate that use of dissolvable tobacco products has been consistently low in youth populations, and that these available survey data do not support literature suggesting dissolvable tobacco products may appeal to youth. However, the provided studies examined the use of a wide array of dissolvable tobacco products, and no data was provided on the characteristics of the dissolvable tobacco products in these studies (e.g., Camel Sticks) to explain how that information could be bridged to the new products. Therefore, you did not demonstrate that the characteristics of the products in these studies are comparable to the new products and that these data can be bridged to the new products that are the subject of these SE Reports. You also refer to the Summary TPSAC report on Dissolvable Tobacco Products, indicating the report states "*there is little use of [dissolvable tobacco products] by youth, even though several products have been on the market for about 10 years*." However, the report also states "*the TPSAC concluded that the available evidence, while limited, leads to a qualitative judgment that availability of DTPs could increase the number of users of tobacco products. This judgment was based on experience with other STs, data presented from the State of Indiana showing that some adolescents were already using DTPs, the survey data on youth perceptions of the products from the State of Virginia, and the potential for youth to be drawn to a novel product*." The information you provided did not demonstrate that the slower release of nicotine in the new products compared to the predicate product do not make the new products more appealing to youth and

inexperienced smokeless tobacco users, and thus do not cause the new products to raise different questions of public health. You needed to provide sufficient scientific evidence and rationale that the differences in nicotine release do not cause the new products to raise different questions of public health. Such evidence could have included information on use behaviors for the new and predicate products. There may be other ways to satisfy this deficiency, and you are responsible for identifying how to best do this.