FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0000273, SE0000275, SE0000279, and SE0000280

SE0000273: Camel Sticks Mint	
Package Type	Plastic can with plastic lid
Package Quantity	5.85 g
Portion Count	12 sticks
Portion Mass	487.4 mg
Portion Length	75 mm
Portion Width	2.9 mm (diameter)
Tobacco Cut Size	(b) (4) µm
Characterizing Flavor	Mint
SE0000275: Viceroy Flex	
Package Type	Pouch (4 pouches in a box)
Package Quantity	12.27 g
Portion Count	12 portions
Portion Mass	1,022.6 mg
Portion Length	15 mm
Portion Width	8 mm (diameter)
Tobacco Cut Size	(b) (4) µm
Characterizing Flavor	None
SE0000279: Camel Strips Mint	
Package Type	Plastic can with plastic lid
Package Quantity	2.88 g
Portion Count	12 strips
Portion Mass	240 mg
Portion Length	32 mm
Portion Width	22 mm
Portion Thickness	0.5 mm
Tobacco Cut Size	(b) (4) µm
Characterizing Flavor	Mint
SE0000280: Camel Orbs Mint	
Package Type	Plastic can with plastic lid
Package Quantity	2.28 g
Portion Count	10 orbs
Portion Mass	228 mg
Portion Length	12 mm
Portion Width	8 mm
Portion Thickness	3 mm
Tobacco Cut Size	(b) (4) µm
Characterizing Flavor	Mint

Common Attributes of SE Reports	
Applicant	R.J. Reynolds Tobacco Company
Report Type	Provisional
Product Category	Smokeless Tobacco
Product Sub-Category	Dissolvable
Recommendation	
Issue Not Substantially Equivalent (NSE) Orders.	

Technical Project Lead (TPL):

Todd L. Cecil -S
Digitally signed by Todd L. Cecil -S
Date: 2020.01.17 11:22:24 -05'00'

Todd L. Cecil, Ph.D.
Associate Director
Division of Product Science
Office of 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: 2020.04.13 16:43:27 -04'00'

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

TABLE OF CONTENTS

1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted two predicate tobacco products in each SE Report.[1] The applicant's rationale for presenting comparisons against two predicate tobacco products is that it believes the new tobacco products can be considered a hybrid of two smokeless tobacco product sub-categories, loose dry snuff and loose moist snuff. The applicant submitted the following predicate tobacco products:

SE0000273: Camel Sticks Mint, SE0000275: Viceroy Flex, SE0000279: Camel Strips Mint, and SE0000280: Camel Orbs Mint	
Product Name	Dental Scotch
Package Type	Can (fiberboard and metal)
Package Quantity	1.15 oz.
Portion Count	Not applicable
Portion Mass	Not applicable
Portion Length	Not applicable
Portion Width	Not applicable
Portion Thickness	Not applicable
Tobacco Cut Size	(b) (4) µm
Characterizing Flavor	None
SE0000273: Camel Sticks Mint, SE0000275: Viceroy Flex, SE0000279: Camel Strips Mint, and SE0000280: Camel Orbs Mint	
Product Name	Grizzly Long Cut Mint
Package Type	Plastic can with plastic lid
Package Quantity	1.2 oz.
Portion Count	Not applicable
Portion Mass	Not applicable
Portion Length	Not applicable
Portion Width	Not applicable
Portion Thickness	Not applicable
Tobacco Cut Size	(b) (4) µm
Characterizing Flavor	Mint

The predicate tobacco products are, respectively, loose dry snuff and loose moist snuff manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 18, 2011, FDA received four original SE Reports (SE0000273, SE0000275, SE0000279, and SE0000280) from R.J. Reynolds Tobacco Company. FDA issued Acknowledgment letters on July 15, 2011. FDA issued Advice/Information Request (A/I) Letters on October 25, 2012. On November 16, 2012, FDA received amendments SE0005100, SE0005102, SE0005106, and

[1] The applicant requested comparison of each new tobacco product to both predicate tobacco products for determination of substantial equivalence; thus, an evaluation was conducted on each new tobacco product compared to each of the two distinct predicate tobacco products separately.

SE0005107. FDA issued a Notification Letter on March 29, 2013,[2] indicating that scientific review would begin on May 15, 2013. In response, FDA received amendments SE0008549, SE0008551, SE0008552, and SE0008553 on May 14, 2013. Following the first round of scientific review, on March 18, 2014, FDA issued an A/I Letter to the applicant, with a response due date of May 17, 2014. In response, FDA received an amendment (SE0010325) on March 26, 2014, requesting a nine-month extension to respond to the March 18, 2014, A/I Letter. FDA issued an Extension Response Letter on March 26, 2014, requesting information to assist the Agency in making an extension decision (e.g., proposed extension date, rationale for request). On April 2, 2014, FDA received amendment SE0010360[3] re-requesting a nine-month extension to respond to the March 2014 A/I Letter. FDA issued an Extension Denial Letter on May 9, 2014. Also on May 9, 2014, FDA issued a General Correspondence letter advising the applicant that scientific review is completed with the predicate tobacco products in place at the start of scientific review. On May 15, 2014, FDA received a request for supervisory review under 21 CFR 10.75 (AP0000010) of the Extension Denial Letter, which also contained a request for an emergency stay of the March 2014 A/I Letter response date (i.e., May 17, 2014). On May 16, 2014, FDA issued a General Correspondence letter: denying the applicant's request for an emergency stay of the March 2014 A/I Letter response date; stating that the Agency intended to commence its next round of scientific review based on the information provided by the applicant as of May 17, 2014; but allowing that, if the Agency granted AP0000010, then the applicant would have additional time to respond to the March 2014 A/I Letter. On May 16, 2014, FDA received an amendment (SE0010498) responding to the March 2014 A/I Letter. FDA issued an Appeal Denial Letter for AP0000010 on February 18, 2015. FDA issued a Preliminary Finding Letter on March 4, 2015. In response, FDA received an amendment (SE0010951) on March 6, 2015 requesting a 60-day extension to respond to the Preliminary Finding Letter. FDA issued an Extension Denial Letter on March 31, 2015. FDA received a request for supervisory review under 21 CFR 10.75 (AP0000013) of FDA's Preliminary Finding Letter on April 3, 2015. FDA issued a Refusal-To-Accept Letter for AP0000013 on May 6, 2015. In response to the Preliminary Finding Letter, FDA received an amendment (SE0011202) on April 3, 2015. On May 14, 2015, FDA received an amendment (SE0011774) to correct errors from the April 3, 2015, amendment regarding Camel Snus Frost. As stated previously in this section of the TPL review, Camel Snus Frost was not identified by the applicant as a predicate tobacco product prior to the start of scientific review and thus was not included in the evaluation of these SE Reports; therefore, the information in the May 14, 2015, amendment was not included in the evaluation of these SE Reports.

[2] A correction to the March 29, 2013, original Notification Letter was issued on April 5, 2013. The April 5, 2013, Notification Letter corrected text from the original Notification Letter, but it did not change the date scientific review was expected to begin.

[3] The April 2, 2014, extension request stated that the applicant believed Camel Snus Frost is the most appropriate predicate tobacco product for all four SE Reports, and, therefore, an extension was needed so that the applicant could provide additional information on that product. However, the Camel Snus Frost product, was not identified in the original SE Reports and was not identified by the applicant as a predicate tobacco product when the applicant amended its SE Reports prior to the start of scientific review in May 2013.

Product Name	SE Report	Amendments
Camel Sticks Mint	SE0000273	SE0005100 SE0008549 SE0010325 SE0010360 SE0010498 SE0010951 SE0011202 SE0011774
Viceroy Flex	SE0000275	SE0005102 SE0008552 SE0010325 SE0010360 SE0010498 SE0010951 SE0011202 SE0011774
Camel Strips Mint	SE0000279	SE0005106 SE0008553 SE0010325 SE0010360 SE0010498 SE0010951 SE0011202 SE0011774
Camel Orbs Mint	SE0000280	SE0005107 SE0008551 SE0010325 SE0010360 SE0010498 SE0010951 SE0011202 SE0011774

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 Marcella White on October 25, 2012, and December 20, 2012.

The final reviews conclude that the SE Reports are administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews to determine whether the applicant established that the predicate tobacco products are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007). The OCE reviews dated May 28, 2013, for SE0000273 and dated May 29, 2013, for SE0000275, SE0000279, and SE0000280 conclude that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco products are grandfathered and, therefore, are eligible predicate tobacco products.[4]

4. SCIENTIFIC REVIEW

Scientific reviews were completed by the Office of Science (OS), in which each new tobacco product is compared to each of two individual predicate tobacco products[5] separately (i.e., the SE review of each new tobacco product was not a composite evaluation); statements in these reviews are intended to apply as such for the following disciplines:

4.1. CHEMISTRY

Chemistry reviews were completed by Shixia Feng on September 20, 2013, and August 18, 2014, and by Tianrong Cheng on June 22, 2015.

The final chemistry review concludes that the new tobacco products have different characteristics related to product chemistry compared to the corresponding predicate tobacco products 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 of your SE Reports show that the storage time for the new products before conducting HPHCs testing is approximately 10 to 20 months longer than that for the corresponding predicate products. All of your SE Reports lack explanation on how the storage time would impact the comparison of HPHC data between the new and predicate products. You stated that the storage time for the new products being tested was longer than the "reasonably expected shelf-life" and could be "considered as a "worst case scenario." Your statement appears to be based on an assumption that, at the time of the HPHC testing, the HPHC levels were the highest/worst for the new products and the lowest/best for the predicate products. You did not provide evidence demonstrating the validity of this assumption. For certain smokeless products, HPHC levels, such as, nicotine may decrease over the shelf-life. A decrease in HPHC level over the storage time for the new and predicate products may affect the percent differences in HPHCs between the new and predicate products and therefore may affect the evaluation outcome. In order for FDA to determine the differences in HPHC levels, that

[4] Addendum reviews were completed on April 20, 2018, to clarify the characterizing flavor of the predicate tobacco products. The addendum reviews do not change the conclusions of the initial grandfather determinations dated May 28, 2013, and May 29, 2013.

[5] For the purposes of this evaluation, Dental Scotch is denoted as predicate tobacco product 1 and Grizzly Long Cut Mint is denoted as predicate tobacco product 2.

represent the difference, between the new and predicate products, provide comparable HPHCs data for the new and predicate product. For example, you could provide HPHC data generated from the new and predicate products that have the same storage time. Alternatively, you could also provide scientific evidence explaining how the storage time would impact the comparison of HPHC data between the new and predicate products for all of your SE Reports.

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

4.2. ENGINEERING

Engineering reviews were completed by Christian Coyle on September 12, 2013, Julie Morabito on August 11, 2014, and Komal Ahuja on June 17, 2015.

The final engineering review concludes that the new tobacco products have different characteristics related to product engineering compared to the corresponding predicate tobacco products 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. For all of your SE Reports, the March 2015 Preliminary Finding letter included a deficiency directing you to provide scientific rationale and discussion to justify why the significant dissimilarities in the product design characteristics of the new and corresponding predicate products do not cause the new products to raise different questions of public health. However, you did not adequately address the deficiency, and therefore, a final determination of substantial equivalence cannot be made with the information you provided. You included comparisons with a grandfather product, Camel Snus Frost, which is not the predicate product included prior to the start of the scientific review process and therefore cannot be used as part of the evaluation. You also include epidemiology studies in an attempt to justify the dissimilarities. However, you do not provide design information to perform a comprehensive engineering evaluation. As such, you have not adequately addressed the significant dissimilarities in the product design characteristics of the new and corresponding predicate products. The new products have the following design characteristics:

    a. Tobacco particle size;
    b. Final moisture;
    c. Final portion weight;
    d. Portion length;
    e. Portion width;
    f. Portion height;
    g. Portion shape; and
    h. Portion density.

In contrast, the predicate products (Dental Scotch and Grizzly Long Cut Mint) have the following design characteristics:

i. Tobacco particle size; and
j. Final moisture.

To address this deficiency, provide scientific discussion and rationale as to why these significant 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.

(b)(5) Deliberative Process Privilege

the applicant did provide tobacco particle size/cut size and final moisture for the new and both predicate tobacco products and the portion physical measurements for the new tobacco products. However, this information indicated that there were differences in tobacco particle size between all the new tobacco products and both the predicate tobacco products; and these differences may lead to an increase in the nicotine availability with an associated increase in nicotine release rate. An increase in release rate of nicotine, associated with an increase in pH may lead to changes in user perceptions. Because the applicant provided pK data rather than dissolution data, the evaluation of the effects of changes to tobacco particle size, final moisture, and portion physical measurements were deferred to behavioral and clinical pharmacology (BCP) for the evaluation of nicotine release rate. There are also differences between the new and predicate tobacco products in terms of % moisture. The applicant did not provide target ranges for % moisture; thus, it is presumed that no variability in the target specifications is expected or tolerated. The new tobacco products in SE0000275 and SE0000279 are stated to contain a higher moisture percentage than predicate tobacco product 1, which may lead to increased microbial activity. The moisture content for these tobacco products were deferred to microbiology for further evaluation. SE0000273 and SE0000280 are stated to contain a decrease in moisture content when compared to both predicate tobacco products. A decrease in the reported moisture content (50% to 1400%) indicate that changes in microbial activity are expected. Therefore, these STNs were deferred to microbiology for further evaluation.

Additionally, each new tobacco product relies on different mechanical release mechanisms than those of the predicate tobacco products. For instance, SE0000275 and SE0000280 rely upon mastication of the new tobacco product medium to provide nicotine release, while the predicate tobacco products rely upon intimate contact between the tobacco filler and the mucus membranes coupled with salivary and mucosal solvation as a means of nicotine transport. The applicant provided information from clinical trials and survey data to address changes in nicotine release rates and format differences in the new tobacco products compared with the predicate

tobacco products. The evaluation of the clinical and survey data was deferred to BCP for further review.

The review by BCP evaluated potential increase in nicotine release rate caused by design parameter differences and has determined that the applicant has not adequately demonstrated that the design changes identified in the engineering review do not cause the new tobacco products to raise different questions of public health. The review by microbiology evaluated the difference in moisture content between the new and predicate tobacco products and has determined that the applicant has not adequately demonstrated that this design change does not cause the new tobacco products to raise different questions of public health. Therefore, I, as TPL, conclude that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products related to product engineering do not cause the new tobacco products to raise different questions of public health.

4.3. MICROBIOLOGY

Microbiology reviews were completed by Michael Koenig on March 13, 2014, August 11, 2014, and June 22, 2015.

The final microbiology review concludes that the new tobacco products have different characteristics related to product microbiology compared to the corresponding predicate tobacco products 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. Your SE Reports require additional aging study information. All of your SE Reports lack aging study information for the predicate products. SE0000273, SE0000279, and SE0000280 include aging study information for the new product, but SE0000275 does not include such information for the new product (Viceroy Flex). Aging study data for the predicate tobacco products and Viceroy Flex are needed. The studies should include *all* of the following parameters, which were included in your aging studies for the Camel Orbs Mint, Camel Sticks Mint, and Camel Strips Mint tobacco products:

    a. pH
    b. Water activity (a_w)
    c. Moisture content
    d. TSNAs (total, NNN, NNK)
    e. Nicotine content
    f. Bacterial load

    Ideally, measurements of these parameters should be made at the beginning, middle, and end of the expected storage time for the products.
    In addition, for all tobacco products, full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for all testing performed are needed. The accuracy, sensitivity, specificity and reproducibility of the test methods should be determined and documented. Additionally, if any of the measurements of aging differ between the new and predicate tobacco products, evidence and a scientific

rationale demonstrating that these differences do not cause the new tobacco products to raise different questions of public health are needed.

The applicant provided percentage moisture data for all of the new and predicate tobacco products. All of the new tobacco products are reported to contain different target moisture content (↓40% to ↑166% relative to predicate tobacco product 1 and ↓70% to ↓94% relative to predicate tobacco product 2). Changes in moisture content may lead to changes in microbial growth during production and storage. Changes in microbial growth are evaluated through changes in TSNA levels and bacterial loads over shelf life of the tobacco products. The applicant provided stability information through aging studies for the new tobacco products in SE0000273, SE0000279, and SE0000280; however, the applicant did not provide stability information (including TSNA levels and bacterial loads) for either of the predicate tobacco products or for the new tobacco product in SE0000275. Without this information, FDA is unable to determine the effects of differences in the engineering parameters or the tobacco product stability during shelf life between the new and corresponding predicate tobacco products. Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding 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 Brian Erkkila on March 12, 2014, February 23, 2015, and July 23, 2015.

The final toxicology review concludes that the new tobacco products in SE0000273, SE0000275, and SE0000279 have different characteristics related to product toxicology compared to the corresponding predicate tobacco products but the differences do not cause the new tobacco products to raise different questions of public health. The review identified the following differences:

- Addition of complex ingredients not present in predicate tobacco products 1 and 2
- Increase in Acetaldehyde (116% and 90%, respectively) and Arsenic (40% and 43%, respectively) compared to predicate tobacco product 2 (SE0000273 and SE0000279)
- Increase in Formaldehyde (28%) compared to predicate tobacco product 2 (SE0000273)

The applicant provided sufficient information regarding the compounds used in making complex purchased ingredients to show that the differences in complex ingredients between the new tobacco products and each predicate tobacco product do not cause the new tobacco products to raise different questions of public health. Furthermore, although there are increases in acetaldehyde and arsenic (SE0000273 and SE0000279) and formaldehyde (SE0000273) in the new tobacco products relative to predicate tobacco product 2, the absolute concentration of these HPHCs measured in the new tobacco products is low enough that delivery of an estimated total daily intake of these HPHCs from the new tobacco products would not cause the new tobacco products to raise different questions of public health from a toxicology perspective. Therefore, the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products in SE0000273, SE0000275, and SE0000279 to raise different questions of public health from a toxicology perspective.

The final toxicology review concludes that the new tobacco product in SE0000280 has different characteristics related to product toxicity compared to the corresponding predicate tobacco products and that the SE Report lacks adequate evidence to demonstrate that the differences do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Addition of complex ingredients not present in predicate tobacco products 1 and 2
- Increase in Acetaldehyde (66%), Arsenic (19%), Formaldehyde (804%), and NNK (12%) compared to predicate tobacco product 2

The applicant provided sufficient information regarding the compounds used in making complex purchased ingredients to show that the differences in complex ingredients between the new tobacco product and each predicate tobacco product do not cause the new tobacco product to raise different questions of public health. Furthermore, although there are increases in acetaldehyde, arsenic and formaldehyde (SE0000280) in the new tobacco product relative to predicate tobacco product 2, the absolute concentration of these HPHCs measured in the new tobacco product is low enough that delivery of an estimated total daily intake of these HPHCs from the new tobacco product would not cause the new tobacco product to raise different questions of public health from a toxicology perspective.

(b)(5) Deliberative Process Privilege

(b)(5) Deliberative Process Privilege

. Based upon the data presented by the applicant in SE0000280, the NNK mean values of the new tobacco product and predicate tobacco product 2 are considered to be substantially equivalent based on a two, one sided t-test. Therefore, the increase in NNK identified in the review is within the typical variability of the analytical method and may represent noise in the measurement rather than an actual increase in NNK in the new tobacco product. Because the NNK measured in the new tobacco product and predicate tobacco

product 2 is considered to be substantially equivalent, the more data to account for uncertainty, variability, nicotine intake, etc. within the QRA are not necessary. No toxicology deficiency remains for SE0000280. Therefore, the differences in characteristics related to product toxicology between the new tobacco product and corresponding predicate tobacco products do not cause the new tobacco product in SE0000280 to raise different questions of public health.

4.5. SOCIAL SCIENCE

Social science reviews were completed by Amber Koblitz on September 10, 2013, August 14, 2014, and July 7, 2015.

The final social science review concludes that the new tobacco products have different characteristics compared to the corresponding predicate tobacco products 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 review identifies the following deficiency that has *not* been adequately resolved:

1. In all of your SE Reports, your response to Deficiency 6 from the March 4, 2015 Preliminary Finding letter provides a data summary to support your assertion that consumer use behavior would not be affected by changes in flavor ingredients, (b)(5) Deliberative P (b)(5) Delib and package size changes in a manner that would cause the new products to raise different questions of public health. You state that HPHC data are similar between the new and predicate products. You also provide comparisons between three of the new products, Camel Sticks Mint (SE0000273), Camel Strips Mint (SE0000279), and Camel Orbs Mint (SE0000280), and one of the predicate products, Grizzly Long Cut Mint. No information from the NTBM was included for Viceroy Flex (SE0000275).

   This information about tobacco use behavior does not sufficiently demonstrate that changes in flavor ingredients, (b)(5) De iberative Process Pri, and package size do not influence tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users when comparing the predicate products to the new products. You provide a summary of comparisons from the National Tobacco Behavior Monitor (NTBM) survey from May 2010 to December 2014 and draw the conclusion that changes in flavor ingredients, (b)(5) Deliberative Process Priv, and package size do not influence tobacco initiation, tobacco recidivism, consumption frequency (portions per day), consumption rate (days of use per week), and intentions to quit tobacco between users of Camel Sticks Mint, Camel Strips Mint, and Camel Orbs Mint compared to Grizzly Long Cut Mint. However, there is not enough information to assess these assertions. Not enough information was included about the NTBM methodology and data analyses to determine whether the summarized comparisons can be used to address this deficiency. You report means and confidence intervals for the direct comparisons between the above referenced products, but do not include inferential statistics. Moreover, the sample sizes reported for comparisons are so small that interpretation must be cautious, and information about the demographic and tobacco use behavior of the samples was missing such as the amount of poly tobacco use in the samples of users in the comparisons. Additionally, it remains unclear whether appropriate statistical analyses were used for small sample sizes. No dataset or analyses were included to support the statements that the new

products do not raise different questions of public health compared to Grizzly Long Cut Mint.

Provide further explanation about the methodology of the NTBM, description of the sample demographics and tobacco use behavior, as well as inclusion of the dataset, syntax, analysis output, and/or any other pertinent information to allow for evaluation of all new products and the summarized data regarding the impact of differences in flavor ingredients, (b)(5) Deliberative Process Priv, and package size to demonstrate that the new products do not raise different questions of public health as compared to the predicate products related to tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users.

The submitted information was not sufficient to address how the stated changes in flavor ingredients and product format would not cause the new tobacco products to raise different questions of public health. The stated changes in product format between the new and corresponding predicate tobacco products include differences in (b)(5) Deliberative Process Pri, package size, and use of the products.[6] FDA needed complete information and rationale for the NTBM and the submitted Oliver paper[7] sample sizes, sample demographic and tobacco use behavior, and data analyses and how they pertain to the new tobacco products. Further, a scientific rationale and evidence was not provided to demonstrate whether flavor ingredients and product format changes between predicate tobacco product 2, Grizzly Long Cut Mint, and the new tobacco products in SE0000273, SE0000279, and SE0000280 affected product consumption frequency and rate, tobacco initiation and recidivism prevalence, or intention to quit all tobacco by users. Additionally, no comparisons were included to predicate tobacco product 1, Dental Scotch, nor was any information submitted addressing the new tobacco product in SE0000275. (b)(5) Deliberative Process Priv [redacted].

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a social science perspective. As discussed in the Behavioral and Clinical Pharmacology section (*see infra* Section 4.6 of this TPL review), because of the overlap between the social science deficiency above and the second and third Behavioral and Clinical Pharmacology deficiencies below, these three deficiencies are consolidated into two deficiencies in the letter-ready deficiencies (*see infra* Section 6).

[6] All of the new tobacco products are smokeless dissolvable tobacco products that are intended to be ingested. Dental Scotch (predicate tobacco product 1) is a form of nasally inhaled snuff. Grizzly Long Cut Mint (predicate tobacco product 2) is a form of moist snuff commonly known as dip which is held as a wad between the cheek and gum. Extra juices from moist snuff are expectorated, and after use the wad is removed and thrown away.

[7] Oliver, A.J., Jensen, J.A., Vogel, R.I., Anderson, A.J., Hatsukami, O.K. (2013) Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. *Nicotine Tob. Res.* Jan: 15(1): 88-92.

The review also evaluated the health information summaries. The applicant originally submitted a health information summary for each SE Report. The first social science review noted that the health information summaries potentially could cause a violation of section 911 of the FD&C Act.[8] In response to the March 18, 2014, deficiency 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 (BCP) reviews were completed by Sarah Evans and Elena Mishina on August 29, 2014, respectively. Combined BCP reviews were completed by Sarah Evans on September 10, 2013, and by Lynn Hull and Lingling Guan on July 16, 2015.[9]

The final combined 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 corresponding predicate tobacco products 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. (b)(5) Deliberative Process Privilege

[8] The March 18, 2014, A/I Letter stated in Deficiency 22 that the submitted Health Information Summaries may violate section 911(b)(2)(A)(i)(II) of the FD&C Act. Deficiency 22 should have stated, however, that the submitted Health Information Summaries may potentially violate section 911(b)(2)(A)(iii) of the FD&C Act.

[9] Each of these reviews addressed both clinical pharmacology and behavioral pharmacology within the review. The 2015 review addressed both clinical pharmacology and behavioral pharmacology within the review, but was authored by a clinical pharmacologist (Lingling Guan) and a behavioral pharmacologist (Lynn Hull).

[10] The differences in ingredients render these tobacco products distinct tobacco products from the new tobacco products under section 910(a)(1)(B) of the FD&C Act.

2. (b)(5) Deliberative Process Privilege

3.

(b)(5) Deliberative Process Privilege

I agree with the second and third deficiencies (except as noted above) in the final combined BCP review; these deficiencies and the deficiency in the social science review[11] overlap somewhat in

[11] See Section 4.5 of this TPL review.

content. The behavioral and clinical pharmacology deficiencies are focused on constituent release differences, especially as they relate to nicotine (constituent) and menthol (flavor and permeation enhancer), and how these differences in constituent release will affect the behavioral and clinical pharmacology of the new and predicate tobacco products. The social science deficiency focused on, among other things, the new and predicate tobacco products' format and how these differences impact consumer perception and use (e.g., intent to try, and cessation) of the tobacco product. The information contained in these reviews, regardless of whether that information was analyzed from the perspective of behavioral and clinical pharmacology or social science, shows that these differences between the new and predicate tobacco products can influence consumer initiation, cessation, dependence, continued use, abuse liability, and perception. The applicant relies on the NTBM survey to support its assertion that these differences in product characteristics between predicate tobacco product 2, Grizzly Long Cut Mint, and the new tobacco products in SE0000273, SE0000279, and SE0000280 do not cause the new tobacco products to raise different questions of public health. However, the NTBM study has several limitations, including a small sample size for these tobacco products and a lack of detail about the statistical treatments that were used in the analysis of the data. Additionally, no comparisons were included to predicate tobacco product 1, Dental Scotch, nor was any information submitted addressing the new tobacco product in SE0000275. Thus, the data provided by the applicant are inadequate to show the applicability of this survey to the new tobacco products and that these differences do not cause the new tobacco products to raise different questions of public health. Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a behavioral and clinical pharmacology perspective. As noted in the Social Science section (*see supra* Section 4.5 of this TPL review), because of the overlap between the social science deficiency and the second and third Behavioral and Clinical Pharmacology deficiencies, these three deficiencies are consolidated into two deficiencies in the letter-ready deficiencies (*see infra* Section 6).

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 an 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 and corresponding predicate tobacco products:

- Different product format (i.e., portioned vs non-portioned, packaged in different quantities, dissolvable vs loose tobacco, etc.), contain different flavor ingredients, and incorporate substantial differences in product design, compared to predicate tobacco products 1 (Dental Scotch) and 2 (Grizzly Long Cut Mint)
- New tobacco products are intended to be ingested, but predicate tobacco products 1 and 2 are not normally ingested[6]

- Different tobacco blends than predicate tobacco products 1 and 2
- New tobacco products contain 19-35 additives compared to predicate tobacco products 1 and 2 which have 0-9 additives
- Higher free nicotine quantity (↑164-960%) compared to predicate tobacco product 1 and lower free nicotine quantity (↓60-90%) compared to predicate tobacco product 2
- Higher NNK quantity (↑12%) compared to predicate tobacco product 2 (SE0000280)
- Increase in formaldehyde compared to predicate tobacco product 2 (SE0000273 and SE0000280)
- Increase in acetaldehyde and arsenic compared to predicate tobacco product 2
- Changes in nicotine release rates, menthol, binders, and coatings compared to predicate tobacco products 1 and 2 (SE0000273 and SE0000279)
- Change in % moisture compared to predicate tobacco products 1 and 2
- Change in tobacco particle size compared to predicate tobacco products 1 and 2

The applicant has failed to demonstrate that the following differences in characteristics do not cause the new tobacco products to raise different questions of public health:

- Increase in free nicotine compared to predicate tobacco product 1
- New tobacco products have changes in nicotine release rates, menthol, binders, and coatings compared to predicate tobacco products 1 and 2
- Changes in product format, flavor, and ingredients compared to predicate tobacco products 1 and 2

The applicant provided two different predicate tobacco products, a dry snuff (predicate tobacco product 1) and a moist snuff (predicate tobacco product 2), which have significantly different characteristics than the new tobacco products (dissolvables in the following portioned formats: pellets (pressed or molded), sticks, and strips). In determining substantial equivalence, a single predicate tobacco product is used for comparison purposes, as a meaningful scientific comparison to determine whether the characteristics of a new tobacco product and a predicate tobacco product are the same or are different but present no different questions of public health cannot be made between a new tobacco product and multiple predicate tobacco products evaluated together. Accordingly, for these SE Reports, FDA evaluated each new tobacco product as compared to each individual predicate tobacco product separately. Furthermore, the applicant has not provided full aging/stability study information or sufficient information on how the differences in storage time would impact the stability of the product and the comparison of HPHC data between the new and predicate tobacco products. Additionally, National Tobacco Behavior Monitor (NTBM) data was submitted for three of the four new tobacco products (Camel Sticks Mint, Camel Strips Mint, and Camel Orbs Mint) to demonstrate that certain differences in characteristics between the three new tobacco products and predicate tobacco product 2 (e.g., product format) do not impact consumer perception and use, and behavioral and clinical pharmacology; however, the NTBM data provided by the applicant are inadequate due to a lack of clarity about the specific statistical methods used and small sample sizes. Additionally, no comparisons were included to predicate tobacco product 1, nor was any information submitted addressing the new tobacco product in SE0000275 (Viceroy Flex). Therefore, the applicant has failed to provide sufficient information to support a finding of substantial equivalence.

The predicate tobacco products meet statutory requirements because it was determined that they are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007).

The chemistry, engineering, microbiology, social science, and behavioral and clinical pharmacology (BCP) reviews conclude that the new tobacco products have different characteristics compared to the individual predicate tobacco products 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. Likewise, the toxicology review concludes that the new tobacco products have different characteristics compared to the individual predicate tobacco products, and that SE0000280 lacks adequate evidence to demonstrate that the differences do not cause the new tobacco product (Camel Orbs Mint) to raise different questions of public health. [redacted]; the applicant did provide tobacco particle size/cut size and final moisture for the new and both predicate tobacco products and the portion physical measurements for the new tobacco products. [redacted] In this case, the increase in NNK should be considered to be within the typical variability of the analytical method and may represent noise in the measurement rather than an actual increase in NNK in the new tobacco product. [redacted] the reported amount of NNN in the new tobacco products is reduced by a large margin and would result in a decreased TSNA exposure for the user relative to each of the predicate tobacco products. [redacted]. However, I concur with the remainder of these reviews and recommend that NSE order letters be issued.

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 SE0000273, SE0000275, SE0000279, and SE0000280, as identified on the cover page of this review. The NSE order letters should include the following text **prior** to their lists of deficiencies:

> Your SE Report includes information for an additional predicate tobacco product (Camel Snus Frost) that you identified in your April 3, 2015, amendment as a predicate tobacco product. Information for this additional predicate tobacco product is provided alongside information for the new and predicate tobacco products identified in the SE Report at the time scientific review commenced. Because the comparison between the new tobacco product and the identified

predicate tobacco product is a fundamental aspect of an SE Report, changing the predicate tobacco product changes the basis of the substantial equivalence evaluation. An applicant may change its predicate tobacco product if scientific review of the application has not yet started. However, once FDA commences scientific review, an applicant should not change its predicate tobacco product(s); the application review will be based on the comparison between the predicate tobacco product(s) in place at the start of scientific review and the new tobacco product. Therefore, the additional predicate tobacco product, Camel Snus Frost, that you identified was not considered in FDA's evaluation of your SE Reports. FDA issued a Notification Letter on March 29, 2013, which notified you that scientific review was scheduled to begin on May 15, 2013; therefore, you had the opportunity to change your predicate tobacco product up to May 14, 2013. You provided an amendment on May 14, 2013, which identified Dental Scotch (dry snuff) and Grizzly Long Cut Mint (moist snuff) as your predicate tobacco products. The deficiencies listed in this letter reflect a comparison of the characteristics of the new tobacco product to the characteristics of each individual predicate tobacco product that you identified at the start of FDA's scientific review, Dental Scotch and Grizzly Long Cut Mint.

6.1. DEFICIENCIES FOR SE0000273

The NSE order letter for SE0000273 should cite the following deficiencies:

1. The length of time between the manufacture of the new tobacco product and the conduct of harmful and potentially harmful constituent (HPHC) testing (18-24 months after manufacture) is approximately 6 to 12 months longer than that for predicate tobacco product 1 (Dental Scotch) and approximately 10 to 12 months longer than that for predicate tobacco product 2 (Grizzly Long Cut Mint). Your SE Report lacked an explanation on how the length of time before testing would impact the comparison of HPHC data between the new and predicate tobacco products. You stated that the length of time between manufacture and testing of the new tobacco product was longer than the "reasonably expected shelf-life" and could be "considered as a "worst case scenario"." Your statement appears to be based on an assumption that, at the time of the HPHC testing, the HPHC levels were the highest/worst for the new tobacco product and the lowest/best for the predicate tobacco products. You did not provide evidence demonstrating the validity of this assumption. For certain smokeless tobacco products, HPHC levels, such as nicotine, may decrease over time. To be able to evaluate and determine the differences in HPHC levels, FDA needed either HPHC data from the new tobacco product and the predicate tobacco products that had comparable lengths of time between their manufacture and their testing, or scientific evidence explaining how different lengths of time between the tobacco products' manufacture and testing would impact the comparison of HPHC data. Without this information, the SE Report lacks adequate evidence to demonstrate that the changes in product design and composition do not cause the new tobacco product to raise different questions of public health.

2. Your SE Report lacks stability or shelf-life study information for the predicate tobacco products. A detailed description of stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed over the complete storage time of the new and each predicate tobacco product was

necessary to assess the new and predicate tobacco products. At a minimum, FDA needed measurements for all of the following for each predicate tobacco product:

a. pH;
b. Water activity (a_w);
c. Moisture content;
d. TSNAs (total, NNN, NNK);
e. Nicotine content; and
f. Bacterial load

Ideally, measurements of these parameters should have been made at the beginning, middle, and end of the expected storage time and at the expected storage conditions of the tobacco products. If any of the measurements of stability had differed between the new and predicate tobacco products, evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health were needed.

3. Your SE Report includes a summary of comparisons from the National Tobacco Behavior Monitor (NTBM) survey from May 2010 to December 2014 which is provided to justify that changes in flavor ingredients and product format do not influence tobacco use behavior between users of the new tobacco product compared to predicate tobacco product 2 (Grizzly Long Cut Mint). However, your SE Report did not include enough information about the NTBM methodology and data analyses to evaluate whether the summarized comparisons can be bridged to your new tobacco product. FDA needed complete information and rationale for the NTBM and the submitted Oliver paper[12] sample sizes, sample demographic and tobacco use behavior, and data analyses and how they pertain to the new tobacco product, such as initiation among non-users, or increased use or decreased cessation among users when comparing the predicate tobacco products to the new tobacco product. Further, a scientific rationale and evidence were needed to demonstrate whether the flavor ingredients and product format changes between predicate tobacco product 2, Grizzly Long Cut Mint, and the new tobacco product affected product consumption frequency and rate, tobacco initiation and recidivism prevalence, or intention to quit all tobacco by users. Additionally, no comparisons were included to predicate tobacco product 1, Dental Scotch. Your SE Report lacked sufficient information to address how the stated change in flavor ingredients and product format would not cause the new tobacco product to raise different questions of public health. Without this information, the SE Report lacks evidence to demonstrate that the differences in flavor ingredients and product format between the new and the predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

4. Your SE Report includes information from clinical trials and survey data to address changes in free nicotine, nicotine release rates, menthol, binders, and coatings in the new tobacco product compared to the predicate tobacco products. However, the “Fresh” predecessor tobacco products used in the clinical studies may be different than the “mint” new tobacco product. Your Product Stewardship Reports note that there are “differences in the

[12] Oliver, A.J., Jensen, J.A., Vogel, R.I., Anderson, A.J., Hatsukami, O.K. (2013) Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. *Nicotine Tob. Res.* Jan: 15(1): 88-92.

ingredients added to [the] tobacco," or that there is a "modified recipe" as compared to the "Fresh"-flavored product. In addition, you suggested that the new tobacco product shared similarities with the Fresh predecessor tobacco products but provided no information or evidence to support this assertion. Therefore, the submitted data cannot be bridged to the new tobacco product. Without the additional data and information, the SE Report lacks adequate evidence to demonstrate that the changes to the product constituents do not cause the new tobacco product to raise different questions of public health.

6.2. DEFICIENCIES FOR SE0000275

The NSE order letter for SE0000275 should cite the following deficiencies:

1. The length of time between the manufacture of the new tobacco product and the conduct of harmful and potentially harmful constituent (HPHC) testing (18-24 months after manufacture) is approximately 6 to 12 months longer than that for predicate tobacco product 1 (Dental Scotch) and approximately 10 to 12 months longer than that for predicate tobacco product 2 (Grizzly Long Cut Mint). Your SE Report lacked an explanation on how the length of time before testing would impact the comparison of HPHC data between the new and predicate tobacco products. You stated that the length of time between manufacture and testing of the new tobacco product was longer than the "reasonably expected shelf-life" and could be "considered as a "worst case scenario"." Your statement appears to be based on an assumption that, at the time of the HPHC testing, the HPHC levels were the highest/worst for the new tobacco product and the lowest/best for the predicate tobacco products. You did not provide evidence demonstrating the validity of this assumption. For certain smokeless tobacco products, HPHC levels, such as nicotine, may decrease over time. To be able to evaluate and determine the differences in HPHC levels, FDA needed either HPHC data from the new tobacco product and the predicate tobacco products that had comparable lengths of time between their manufacture and their testing, or scientific evidence explaining how different lengths of time between the tobacco products' manufacture and testing would impact the comparison of HPHC data. Without this information, the SE Report lacks adequate evidence to demonstrate that the changes in product design and composition do not cause the new tobacco product to raise different questions of public health.

2. Your SE Report lacks stability or shelf-life study information for the new and predicate tobacco products. A detailed description of stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed over the complete storage time of the new and each predicate tobacco product was necessary to assess the new and predicate tobacco products. At a minimum,

FDA needed measurements for all of the following for the new and each predicate tobacco product:

a. pH;
b. Water activity (a_w);
c. Moisture content;
d. TSNAs (total, NNN, NNK);
e. Nicotine content; and
f. Bacterial load

Ideally, measurements of these parameters should have been made at the beginning, middle, and end of the expected storage time and at the expected storage conditions of the tobacco products. If any of the measurements of stability had differed between the new and predicate tobacco products, evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health were needed.

3. Your SE Report includes a summary of comparisons from the National Tobacco Behavior Monitor (NTBM) survey from May 2010 to December 2014 which is provided to justify that changes in flavor ingredients and product format do not influence tobacco use behavior between users of the new tobacco products in SE0000273, SE0000279, and SE0000280 compared to predicate tobacco product 2 (Grizzly Long Cut Mint). However, your SE Report did not include enough information about the NTBM methodology and data analyses to evaluate whether the summarized comparisons can be bridged to your new tobacco products in SE0000273, SE0000279, and SE0000280. Further, no comparisons were included to predicate tobacco products 1 or 2, for your new tobacco product in SE0000275. FDA needed complete information and rationale for the NTBM and the submitted Oliver paper[13] sample sizes, sample demographic and tobacco use behavior, and data analyses and how they pertain to the new tobacco product, such as initiation among non-users, or increased use or decreased cessation among users when comparing the predicate tobacco products to the new tobacco product. Your SE Report was not sufficient to address how the stated change in flavor ingredients and product format would not cause the new tobacco product to raise different questions of public health. Without this information, the SE Report lacks evidence to demonstrate that the differences in flavor ingredients and product format do not cause the new tobacco product to raise different questions of public health as compared to the predicate tobacco products related to tobacco use behavior.

4. Your SE Report includes information from clinical trials and survey data to address changes in free nicotine, nicotine release rates, menthol, binders, and coatings in the new tobacco products in SE0000273, SE0000279, and SE0000280 compared to the predicate tobacco products. However, the "Fresh" predecessor tobacco products used in the clinical studies may be different than the "mint" new tobacco products in SE0000273, SE0000279, and SE0000280. No data was provided for the new tobacco product Viceroy Flex (SE0000275) and you suggested that the new tobacco product shared similarities with the Fresh predecessor tobacco products but provided no information or evidence to support this

[13] Oliver, A.J., Jensen, J.A., Vogel, R.I., Anderson, A.J., Hatsukami, O.K. (2013) Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. *Nicotine Tob. Res.* Jan: 15(1): 88-92.

assertion. Therefore, the submitted data cannot be bridged to the new tobacco product. Without the additional data and information, the SE Report lacks adequate evidence to demonstrate that the changes to the product constituents do not cause the new tobacco product to raise different questions of public health.

6.3. DEFICIENCIES FOR SE0000279

The NSE order letter for SE0000279 should cite the following deficiencies:

1. The length of time between the manufacture of the new tobacco product and the conduct of harmful and potentially harmful constituent (HPHC) testing (18-24 months after manufacture) is approximately 6 to 12 months longer than that for predicate tobacco product 1 (Dental Scotch) and approximately 10 to 12 months longer than that for predicate tobacco product 2 (Grizzly Long Cut Mint). Your SE Report lacked an explanation on how the length of time before testing would impact the comparison of HPHC data between the new and predicate tobacco products. You stated that the length of time between manufacture and testing of the new tobacco product was longer than the "reasonably expected shelf-life" and could be "considered as a "worst case scenario"." Your statement appears to be based on an assumption that, at the time of the HPHC testing, the HPHC levels were the highest/worst for the new tobacco product and the lowest/best for the predicate tobacco products. You did not provide evidence demonstrating the validity of this assumption. For certain smokeless tobacco products, HPHC levels, such as nicotine, may decrease over time. To be able to evaluate and determine the differences in HPHC levels, FDA needed either HPHC data from the new tobacco product and the predicate tobacco products that had comparable lengths of time between their manufacture and their testing, or scientific evidence explaining how different lengths of time between the tobacco products' manufacture and testing would impact the comparison of HPHC data. Without this information, the SE Report lacks adequate evidence to demonstrate that the changes in product design and composition do not cause the new tobacco product to raise different questions of public health.

2. Your SE Report lacks stability or shelf-life study information for the predicate tobacco products. A detailed description of stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed over the complete storage time of the new and each predicate tobacco product was necessary to assess the new and predicate tobacco products. At a minimum, FDA needed measurements for all of the following for each predicate tobacco product:

    a. pH;
    b. Water activity (a_w);
    c. Moisture content;
    d. TSNAs (total, NNN, NNK);
    e. Nicotine content; and
    f. Bacterial load

    Ideally, measurements of these parameters should have been made at the beginning, middle, and end of the expected storage time and at the expected storage conditions of the tobacco products. If any of the measurements of stability had differed between the new

and predicate tobacco products, evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health were needed.

3. Your SE Report includes a summary of comparisons from the National Tobacco Behavior Monitor (NTBM) survey from May 2010 to December 2014 which is provided to justify that changes in flavor ingredients and product format do not influence tobacco use behavior between users of the new tobacco product compared to predicate tobacco product 2 (Grizzly Long Cut Mint). However, your SE Report did not include enough information about the NTBM methodology and data analyses to evaluate whether the summarized comparisons can be bridged to your new tobacco product. FDA needed complete information and rationale for the NTBM and the submitted Oliver paper[14] sample sizes, sample demographic and tobacco use behavior, and data analyses and how they pertain to the new tobacco product, such as initiation among non-users, or increased use or decreased cessation among users when comparing the predicate tobacco products to the new tobacco product. Further, a scientific rationale and evidence were needed to demonstrate whether the product format, flavor ingredients, and package quantity changes between predicate tobacco product 2, Grizzly Long Cut Mint, and the new tobacco product affected product consumption frequency and rate, tobacco initiation and recidivism prevalence, or intention to quit all tobacco by users. Additionally, no comparisons were included to predicate tobacco product 1, Dental Scotch. Your SE Report was not sufficient to address how the stated change in flavor ingredients and product format would not cause the new tobacco product to raise different questions of public health. Without this information, the SE Report lacks evidence to demonstrate that the differences in flavor ingredients and product format do not cause the new tobacco product to raise different questions of public health as compared to the predicate tobacco products related to tobacco use behavior.

4. Your SE Report includes information from clinical trials and survey data to address changes in free nicotine, nicotine release rates, menthol, binders, and coatings in the new tobacco product compared to the predicate tobacco products. However, the “Fresh” predecessor tobacco products used in the clinical studies may be different than the “mint” new tobacco product. Your Product Stewardship Reports note that there are “differences in the ingredients added to [the] tobacco,” or that there is a “modified recipe” as compared to the “Fresh”-flavored product. In addition, you suggested that the new tobacco product shared similarities with the Fresh predecessor tobacco products but provided no information or evidence to support this assertion. Therefore, the submitted data cannot be bridged to the new tobacco product. Without the additional data and information, the SE Report lacks adequate evidence to demonstrate that the changes to the product constituents do not cause the new tobacco product to raise different questions of public health.

[14] Oliver, A.J., Jensen, J.A., Vogel, R.I., Anderson, A.J., Hatsukami, O.K. (2013) Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. *Nicotine Tob. Res.* Jan: 15(1): 88-92.

6.4. DEFICIENCIES FOR SE0000280

The NSE order letter for SE0000280 should cite the following deficiencies:

1. The length of time between the manufacture of the new tobacco product and the conduct of harmful and potentially harmful constituent (HPHC) testing (18-24 months after manufacture) is approximately 6 to 12 months longer than that for predicate tobacco product 1 (Dental Scotch) and approximately 10 to 12 months longer than that for predicate tobacco product 2 (Grizzly Long Cut Mint). Your SE Report lacked an explanation on how the length of time before testing would impact the comparison of HPHC data between the new and predicate tobacco products. You stated that the length of time between manufacture and testing of the new tobacco product was longer than the "reasonably expected shelf-life" and could be "considered as a "worst case scenario"." Your statement appears to be based on an assumption that, at the time of the HPHC testing, the HPHC levels were the highest/worst for the new tobacco product and the lowest/best for the predicate tobacco products. You did not provide evidence demonstrating the validity of this assumption. For certain smokeless tobacco products, HPHC levels, such as nicotine, may decrease over time. To be able to evaluate and determine the differences in HPHC levels, FDA needed either HPHC data from the new tobacco product and the predicate tobacco products that had comparable lengths of time between their manufacture and their testing, or scientific evidence explaining how different lengths of time between the tobacco products' manufacture and testing would impact the comparison of HPHC data. Without this information, the SE Report lacks adequate evidence to demonstrate that the changes in product design and composition do not cause the new tobacco product to raise different questions of public health.

2. Your SE Report lacks stability or shelf-life study information for the predicate tobacco products. A detailed description of stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed over the complete storage time of the new and each predicate tobacco product was necessary to assess the new and predicate tobacco products. At a minimum, FDA needed measurements for all of the following for each predicate tobacco product:

    a. pH;
    b. Water activity (a_w);
    c. Moisture content;
    d. TSNAs (total, NNN, NNK);
    e. Nicotine content; and
    f. Bacterial load

    Ideally, measurements of these parameters should have been made at the beginning, middle, and end of the expected storage time and at the expected storage conditions of the tobacco products. If any of the measurements of stability had differed between the new and predicate tobacco products, evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health were needed.

3. Your SE Report includes a summary of comparisons from the National Tobacco Behavior Monitor (NTBM) survey from May 2010 to December 2014 which is provided to justify that changes in flavor ingredients and product format do not influence tobacco use behavior between users of the new tobacco product compared to predicate tobacco product 2 (Grizzly Long Cut Mint). However, your SE Report did not include enough information about the NTBM methodology and data analyses to evaluate whether the summarized comparisons can be bridged to your new tobacco product. FDA needed complete information and rationale for the NTBM and the submitted Oliver paper[15] sample sizes, sample demographic and tobacco use behavior, and data analyses and how they pertain to the new tobacco product, such as initiation among non-users, or increased use or decreased cessation among users when comparing the predicate tobacco products to the new tobacco product. Further, a scientific rationale and evidence were needed to demonstrate whether the product format, flavor ingredients, and package quantity changes between predicate tobacco product 2, Grizzly Long Cut Mint, and the new tobacco product affected product consumption frequency and rate, tobacco initiation and recidivism prevalence, or intention to quit all tobacco by users. Additionally, no comparisons were included to predicate tobacco product 1, Dental Scotch. Your SE Report was not sufficient to address how the stated change in flavor ingredients and product format would not cause the new tobacco product to raise different questions of public health. Without this information, the SE Report lacks evidence to demonstrate that the differences in flavor ingredients and product format do not cause the new tobacco product to raise different questions of public health as compared to the predicate tobacco products related to tobacco use behavior.

4. Your SE Report includes information from clinical trials and survey data to address changes in free nicotine, nicotine release rates, menthol, binders, and coatings in the new tobacco product compared to the predicate tobacco products. However, the “Fresh” predecessor tobacco products used in the clinical studies may be different than the “mint” new tobacco product. Your Product Stewardship Reports note that there are “differences in the ingredients added to [the] tobacco,” or that there is a “modified recipe” as compared to the “Fresh”-flavored product. In addition, you suggested that the new tobacco product shared similarities with the Fresh predecessor tobacco products but provided no information or evidence to support this assertion. Therefore, the submitted data cannot be bridged to the new tobacco product. Without the additional data and information, the SE Report lacks adequate evidence to demonstrate that the changes to the product constituents do not cause the new tobacco product to raise different questions of public health.

[15] Oliver, A.J., Jensen, J.A., Vogel, R.I., Anderson, A.J., Hatsukami, O.K. (2013) Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. *Nicotine Tob. Res.* Jan: 15(1): 88-92.