FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0000122

SE0000122: Camel Snus Frost	
Package Type	Tin Can and Lid
Package Quantity	8.49 grams/tin
Portion Count	15 pouches
Portion Mass	600 mg/pouch
Portion Length	36.8 mm
Portion Width	12.5 mm
Portion Thickness	6.1 mm
Tobacco Cut Size	(b) (4) [redacted]
Characterizing Flavor	Menthol
Common Attributes of SE Reports	
Applicant	R.J. Reynolds Tobacco Company
Report Type	Provisional
Product Category	Smokeless Tobacco Product
Product Sub-Category	Portioned Snus
Recommendation	
Issue a Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

Kenneth Taylor -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kenneth Taylor -S, 0.9.2342.19200300.100.1.1=1300163932
Date: 2018.10.04 10:31:55 -04'00'

Kenneth M. Taylor, Ph.D.
Chemistry Branch Chief
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: 2018.10.04 14:12:20 -04'00'

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

TABLE OF CONTENTS

1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCT

The applicant submitted the following predicate tobacco product:

SE0000122: Camel Snus Frost	
Product Name	Camel Snus Frost
Package Type	Tin Can and Lid
Package Quantity	7.46 grams/tin
Portion Count	20 pouches
Portion Mass	400 mg/pouch
Portion Length	28.8 mm
Portion Width	11.9 mm
Portion Thickness	6.1 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Spearmint

The predicate tobacco product is a portioned snus smokeless tobacco product manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 15, 2011, FDA received an SE Report from R.J. Reynolds Tobacco Company. FDA issued an Acknowledgement letter to the applicant on July 29, 2011. On June 15, 2012, FDA received an amendment (SE0004573) from the applicant, in response to FDA's request to confirm the list of products for SE Reports which the applicant submitted on or before March 22, 2011. On November 2, 2012, FDA received a response to FDA's October 4, 2012, Advice/Information Request (A/I) letter (SE0005075). On September 13, 2012, a Public Health Impact (PHI) review was completed for this SE Report. FDA assigned SE0000122 to PHI Tier 1. On September 6, 2013, FDA received a response to FDA's May 10, 2013, PHI A/I letter (SE0009731). A detailed review of the product composition prompted FDA to reassign the product to PHI Tier 2 on October 23, 2013. On August 27, 2014, FDA received an unsolicited amendment (SE0010815), containing the applicant's response to CTP's rescission of the refusal to accept decision on an Exemption Request (EX REQ) for this product. In the rescission letter, FDA notified the applicant the new tobacco product was determined to be eligible for the EX REQ pathway, but that the pending SE review would first need to be completed prior to completing review of the applicant's EX REQ. On August 28, 2014, FDA issued a Notification letter to inform the applicant that scientific review of the SE Report would commence on October 12, 2014. FDA issued an A/I letter on May 23, 2016. On June 23, 2016, FDA received amendment SE0013456, containing the applicant's request for additional time to respond to the A/I letter. FDA issued an Extension Granted letter on July 12, 2016, providing the applicant additional time to respond by October 17, 2017. On October 17, 2017, FDA received the applicant's response to the A/I letter (SE0014380) and a request for a claim of categorical exclusion. FDA issued a Preliminary Finding (PFind) letter on

January 5, 2018. On January 5, 2018, FDA received an email from the applicant to clarify a question in the PFind letter. FDA re-issued the PFind letter on January 26, 2018, to clarify the information requested by the applicant. On February 23, 2018, FDA received the applicant's response to the PFind letter (SE0014552). FDA issued a PFind letter on April 30, 2018. On May 9, 2018 and May 17, 2018, FDA conducted teleconferences with the applicant to clarify information requested by the applicant. On May 14, 2018, FDA received an amendment (SE0014719), containing the applicant's request for additional time to respond to the PFind letter. On June 5, 2018, FDA received the applicant's request to withdraw the request for additional time to respond to the PFind letter (SE0014748). FDA re-issued the PFind letter on May 31, 2018, to clarify the information requested by the applicant. On June 28, 2018, FDA received the applicant's response to the PFind letter (SE0014799).

Product Name	SE Report	Amendments
Camel Snus Frost	SE0000122	SE0004573 SE0005075 SE0009731 SE0010815 SE0013456 SE0014380 SE0014552 SE0014719 SE0014748 SE0014799

1.3. SCOPE OF REVIEW

This review captures all regulatory, compliance, and scientific reviews completed for this SE Report.

2. REGULATORY REVIEW

Regulatory reviews were completed by Marcella White on October 4, 2012, and December 20, 2012, and by Jennifer Schmitz on October 19, 2017, and September 21, 2018.

The final review concludes that the SE Report is 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 other than exclusively in test markets as of February 15, 2007). The OCE review dated November 05, 2014, concludes 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.[1]

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 An Vu on January 11, 2015, and by Jiu Ai on December 01, 2017, and August 10, 2018.

The final chemistry review concludes that the new tobacco product has different characteristics related to product chemistry compared to the predicate tobacco product, but the differences do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- 50% increase in portion mass (40% increase in tobacco and non-tobacco ingredients and increased pouch material) and 25% decrease in portion counts per tin
- 8.7% higher amount of (b)(4) and a 6.7% lower amount of (b)(4) on a per gram basis
- Change to (b)(4) from (b)(4) as a pH adjuster
- Change to (b)(4) from (b)(4)

The new tobacco product uses more tobacco on a per portion basis and a different tobacco blend. The tobacco quantity and tobacco blend changes can affect HPHC yields in the new tobacco product and raise different questions of public health. The applicant re-manufactured both the new and predicate tobacco products according to the original design specifications and performed harmful and potentially harmful constituent (HPHC) testing on both products within 10 days of manufacture. The quantities of HPHCs (NNK, NNN, and nicotine) in the new tobacco product are either equivalent or lower than the predicate tobacco product on per gram of product basis. However, on a per portion basis, NNN is increased 67% and NNK is increased 28% in the new tobacco product. The new tobacco product also substitutes the sweetener (b)(4) and the pH adjuster (b)(4) to replace (b)(4) and (b)(4) in similar quantities. Determining whether the tobacco and non-tobacco ingredient changes cause the new tobacco product to raise different questions of public health was deferred to the toxicology review. In response to an engineering deficiency[2] that the increased portion length of the new tobacco product could affect constituent release from the pouch, the applicant submitted nicotine dissolution profiles for the new and predicate tobacco products. Although the dissolution profile of the new tobacco product is different than that of the predicate tobacco product, the released nicotine quantity from the new tobacco product is lower than that of the predicate tobacco product. Therefore, the reduced nicotine release from the new tobacco

[1] An addendum review was completed on April 20, 2018, for the inclusion of characterizing flavor. The addendum review does not change the conclusion of the initial determination.

product demonstrates that the increase in portion size and amount of pouch material does not cause the new tobacco product 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 chemistry perspective.

4.2. ENGINEERING[3]

Engineering reviews were completed by Julie Morabito on December 24, 2014, December 08, 2017[4], and April 27, 2018.

The final engineering review identifies that the new tobacco product has different characteristics related to product engineering compared to the predicate tobacco product. The review identified the following differences:[2]

- Increased pouch size (5% increase in portion width[5] and 27.8% portion length)
- Increased (7.4%) pouch material basis weight

The engineering review concludes that the 5% increase in portion width does not cause the new tobacco product to raise different questions of public health, but the 27.8% increase in portion length may affect constituent dissolution from the pouch. The applicant submitted nicotine dissolution data for the new and predicate tobacco products (see section 4.1 of this review). The nicotine dissolution data, as reviewed by chemistry, demonstrate that the increase in portion length of the new tobacco product does not cause the new tobacco product to raise different questions of public health. Similarly, as demonstrated by nicotine dissolution from the new tobacco product, the increased basis weight of the pouch material is expected to reduce the release of HPHCs from the new tobacco product and therefore does not cause different questions of public health.

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

[2] See April 27, 2018 engineering review.

[3] The engineering review does not provide a conclusion regarding substantial equivalence for key design differences between the new and predicate product. The first engineering review identifies that the new product differs from the predicate product with increased portion mass, difference in pouch material, increased pouch size, and differences in tobacco blend and ingredient levels. The third engineering review identifies that the new product has increased portion thickness, portion length (e.g. pouch size) and pouch material basis weight.

[4] Review was amended on January 25, 2018 to revise Deficiency 2 to require the applicant to clarify discrepancies between the measured values and the originally provided target specifications provided for portion width for the new and predicate tobacco products.

[5] The April 27, 2018, engineering review incorrectly states that there is a 5% increase in portion thickness. This statement is in error. There is a 5% increase in the portion width of the new tobacco product, which is captured correctly in Table 3 of the review.

4.3. MICROBIOLOGY

Microbiology reviews were completed by Almaris Alonso on December 23, 2014, and by David Craft on December 04, 2017.

The final microbiology review concludes that the new tobacco product has different characteristics related to product microbiology compared to the predicate tobacco product but the differences do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Greater decreases in pH (9% vs 2%), moisture content (11% vs 1%) and water activity (11% vs 0.1%) during product storage time
- Greater decreases in NNN (6% vs 4%), NNK (23% vs 4%) and total TSNAs (10% vs 3%) during product storage time
- Decrease in Nitrite (71%) for the new product vs. a 9% increase in the predicate product during product storage time
- Decrease in TAMC (98%) at the beginning of product storage time

Stability data (pH, moisture content (OV%), water activity (a_w), nitrate, nitrite, NNN, NNK, TSNAs, and microbial counts (TAMC and TYMC)) for the new tobacco product was measured at 0, 5, 9, 12, and 14 months, whereas the predicate tobacco product was measured at 0, 2, and 4 months. Since the stability testing time points were different between the new and predicate tobacco products, the new and predicate tobacco product's stability data were compared only at time zero. The nitrite, NNN (54%), NNK (60%) and total TSNAs (45%) levels of the new tobacco product are higher at time zero in comparison to the predicate tobacco product. The differences in nitrite, NNN, NNK and total TSNAs of the new tobacco product in comparison to the predicate tobacco product at time zero are significant from a microbiology perspective. However, this concern is offset by the greater decreases in nitrite (71%), NNN (6%), NNK (23%) and total TSNAs (10%) levels of the new tobacco product than the predicate product during entire product storage time. Additionally, the TAMC of the new tobacco product decreased substantially (98%) when compared to the predicate tobacco product at time zero. The heat treatment resulted in substantial reduction in TAMC of the new tobacco product (5,800,000 colony forming units (cfu) per gram before heat treatment to <10 cfu/g after heat treatment) and predicate tobacco product (3,800,000 cfu/g before heat treatment to approximately 19 cfu/g after heat treatment). Therefore, the higher amounts of nitrite, NNN, NNK and total TSNAs of the new tobacco product in comparison to the predicate tobacco product at time zero are not of concern. Additionally, the microbial count data show a 4% decrease in TAMC and no change in TYMC over the storage time of 15 months for the new tobacco product, indicating that the product is microbially stable. This data shows that even though the water activity (a_w) levels are in a range that would support bacterial and mold growth, the greater decreases in both a_w and moisture content of the new tobacco product compared to the predicate tobacco product are not a concern. The pH decreases in both the new and predicate tobacco products during storage are small and therefore, do not present a concern.

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

4.4. TOXICOLOGY

Toxicology reviews were completed by Susan Chemerynski on December 22, 2015, and by Jonathan Fallica on January 03, 2018.

The final toxicology review concludes that the new tobacco product has different characteristics related to product toxicology compared to the predicate tobacco product, but the differences do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Increased pouch size from 400 mg to 600 mg
- (b)(4) replaces (b)(4)
- (b)(4) replaces (b)(4)
- Increases in (b)(4)
- Increases in formaldehyde, crotonaldehyde, arsenic, cadmium, NNN, and NNK

The ingredient increases (b)(4) appear to be proportional to the nominal 50% increase in the new product pouch size. Additionally, the ingredient substitutions of (b)(4) and (b)(4) in the new tobacco product are not a concern. To demonstrate that these ingredient differences do not cause the new tobacco product to raise different questions of public health, the applicant provided quantitative comparisons of daily intake values for these ingredients based upon consumption of 15 units per day (one package per day). Ingredient exposure estimates were then compared to available published acceptable daily intake (ADI) or possible average daily intake (PADI) values based upon dietary consumption. The exposure estimates for the ingredients in the new tobacco products were determined to be below the ADI or PADI values. Therefore, the ingredient changes do not cause the new tobacco product to raise different questions of public health. The applicant also provided HPHC data for the remanufactured new and predicate tobacco products. On a per gram of tobacco basis, the different HPHC levels do not cause toxicological concerns.

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

4.5. SOCIAL SCIENCE

Social Science reviews were completed by Katherine Margolis on January 06, 2015, and by Elisabeth Donaldson on December 08, 2017, and December 21, 2017[6].

[6] Amendment to the December 8, 2017 Social Science review which incorrectly cited the Office of Science memorandum on product quantity changes (footnote 6). This amendment incorrectly states that the Social Science review was signed on December 7, 2017. The memorandum was signed on December 8, 2017.

The final social science review concludes that the new tobacco product has different characteristics from the predicate tobacco product, but the differences do not cause the new tobacco product to raise different questions of public health from a social science perspective. The review identified the following differences:

- Larger portion mass (600 mg/pouch)
- Larger package quantity (8.49 grams)
- Reduced portion quantity (15 pouches)

The applicant provided the results from an online survey of 5,039 adult current, former and never cigarette smokers. The applicant noted that there were no statistically significant differences in the mean purchase intent ratings, risk perceptions, and appeal for respondents viewing the new tobacco product with those respondents viewing the predicate tobacco product. The applicant also provided two references on clinical studies of snus use by former smokers. Although the social science review mentions that the findings may not apply to the entire general population, the totality of the studies suggest that on a mass-per-day basis, use of the new tobacco product may not be different from the predicate tobacco product. Additionally, OS has determined that, based upon current available evidence, changes in product quantity and portion count do not raise different questions of public health.[7]

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

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. In response to the May 23, 2016 deficiency letter, the applicant indicated that it would instead provide any health information related to the new tobacco products upon request by any party.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act for this provisional SE Report (SE0000122) 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.

[7] Office of Science Memorandum "Product quantity changes in Substantial Equivalence Reports (SE Reports) for statutorily regulated tobacco products," December 7, 2017.

6. CONCLUSION AND RECOMMENDATION

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

- 50% increase in portion mass (from 400 mg to 600 mg)
- 8.7% higher amount of [redacted] and a 6.7% lower amount of (b)(4) on a per gram basis
- Change to (b)(4) from (b)(4) as a pH adjuster
- Change to (b)(4) from (b)(4)
- Increased pouch size (5% increase in portion width and 27.8% portion length)
- 7.4% increase in pouch material basis weight
- Greater decreases in pH (9% vs 2%), moisture content (11% vs 1%) and water activity (11% vs 0.1%) during product storage time
- Greater decreases in NNN (6% vs 4%), NNK (23% vs 4%) and total TSNAs (10% vs 3%) during product storage time
- Decrease in Nitrite (71%) for the new tobacco product vs. a 9% increase in the predicate tobacco product during product storage time
- 98% decrease in TAMC at the beginning of product storage time
- 25% reduced portion quantity
- Increases in (b)(4)
- Increases in formaldehyde, crotonaldehyde, arsenic, cadmium, NNN, and NNK

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health. The larger portion size, which includes the use of more tobacco, can affect the amount of HPHCs in the new tobacco product. The applicant remanufactured both the new and predicate tobacco products and provided HPHC data. On a per gram of tobacco basis, the increases in HPHCs of the new tobacco product are not significant. Additionally, the new tobacco product has an increase in pouch length, which could affect the amount of HPHCs released. The pouch material used in the new tobacco product has a higher basis weight than the pouch material of the predicate tobacco product, which is expected to reduce the release of HPHCs from the new tobacco product. The applicant provided nicotine release dissolution study data. Although the dissolution profile of the new tobacco product is different than that of the predicate tobacco product, the released nicotine quantities from the new tobacco product are lower than that of the predicate tobacco product. Therefore, the changes in pouch size and material do not cause the new tobacco product to raise different questions of public health. Additionally, microbial count data is significantly less at the beginning of storage time for the new tobacco product compared to the predicate tobacco product. During storage, the new tobacco product has greater decreases in water activity and moisture than the predicate tobacco product. As a result, microbial activity is expected to have greater reduction with time in the new tobacco product compared to the predicate tobacco product. The new tobacco product has greater reductions in NNN, NNK, total TSNAs, and nitrite than the predicate tobacco product during storage. The change to (b)(4) and (b)(4) as sweetener and pH adjuster, respectively, are not a concern because these are ingredient substitutions and are below ADI/PADI values. Similarly, increases in (b)(4) in the new tobacco product are due to the increased pouch size, but are still below ADI and PADI amounts and therefore are not a concern. Finally, there is no conclusive data that demonstrate that the increased

size of the new tobacco product portion size or change in portion quantity will affect consumer use of the new tobacco product. Therefore, the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

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).

Because the proposed action is issuing an SE order for the provisional SE Report, it is a class of action that is categorically excluded under 21 CFR 25.35(a). 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.

An SE order letter should be issued for the new tobacco product in SE0000122, as identified on the cover page of this review.