FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0015556

SE0015556: CopenhagenLong Cut	
Package Type	Fiberboard Can and Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b)(4) Cuts Per Inch (CPI)
Characterizing Flavor	None
Attributes of SE Report	
Applicant	U.S. Smokeless Tobacco Company LLC
Report Type	Regular
Product Category	Smokeless Tobacco Products
Product Sub-Category	Loose Moist Snuff
Recommendation	
Issue a Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

Digitally signed by Gloria J. Kulesa -S
Date: 2020.07.21 15:15:57 -04'00'

Gloria Kulesa
Engineering 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: 2020.07.21 15:43:44 -04'00'

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

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1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCT

The applicant submitted the following predicate tobacco product:

SE0015556: Copenhagen Long Cut	
Product Name	Copenhagen Long Cut
Package Type	Fiberboard Can and Metal Lid
Package Quantity	34.02grams
Tobacco Cut Size	(b)(4) CPI
Characterizing Flavor	None

The predicate tobacco product is a loose moist snuff, smokeless tobacco product manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

FDA received the SE Report (SE001556) from Altria Client Services LLC (ALCS), on behalf of U.S. Smokeless Tobacco Company LLC (USSTC) on November 4, 2019. FDA issued an Acceptance letter on November 8, 2019. FDA issued a Deficiency letter on January 31, 2020. On April 7, 2020, FDA received the applicant's response to the Deficiency letter (SE0015848).

Product Name	Original SE Report	Amendment
Copenhagen Long Cut	SE0015556	SE0015848

1.3. SCOPE OF REVIEW

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

2. REGULATORY REVIEW

A regulatory review was completed by Jessica Kiser on November 8, 2019. The review concludes that the SE Report is administratively complete.

3. COMPLIANCE REVIEW

The predicate tobacco product in SE0015556 was determined to be substantially equivalent by FDA under SE0015104. Therefore, this product is an eligible predicate tobacco product.

The Office of Compliance and Enforcement (OCE) completed a review to determine whether the new tobacco product is in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act) (see section 910(a)(2)(A)(i)(II) of the FD&C Act). The OCE reviews dated January 29, 2020 and July 2, 2020, conclude that the new tobacco product is in compliance with the FD&C Act.

4. SCIENTIFIC REVIEW

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

4.1. CHEMISTRY

Chemistry reviews were completed by Mimy Young on December 19, 2019 and by Scott Wasdo on June 5, 2020.

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:

- Tobacco blend:
  - ↓10% total tobacco
  - ↓11% (b) (4) tobacco
    - ↓13% [redacted]
  - ↓11% (b) (4) tobacco
    - ↓11% [redacted]
    - ↓11% [redacted]
  - ↓10% (b) (4) tobacco
  - Presence of [redacted] tobacco [redacted] mg/g)
  - ↓10% [redacted] tobacco
- Presence of [redacted] mg/g)
- Replacement of [redacted] with [redacted] in container closure system
- Decrease in flavor ingredients (e.g., [redacted] [10%], [redacted] [9%])
- Presence of binder ingredients [redacted] mg/g [redacted]; [redacted] mg/g [redacted] m/g [redacted]; decrease (b) (4) (b) (4) [↓9%])
- Decrease in total nicotine (↓13%), free nicotine (↓10%), cadmium (↓16%), B[a]P (↓13%), NNN (↓6%), NNK (↓5%)
- Increase in acetaldehyde (↑18%)

The new tobacco product contains decreased levels of total and individual tobacco blends (10-13%) and the addition of (b) (4) tobacco that is not present in the predicate tobacco product. While the (b) (4) tobacco composition is identical between the new and predicate tobacco products, the differences in the (b) (4) tobacco blend quantities contribute to minor differences in the finished product weight. The new tobacco product contains lower quantities of [redacted], and [redacted]. Also, the new tobacco product contains [redacted] and [redacted] that is not present in the predicate tobacco product. These ingredient differences were deferred to toxicology. Harmful and potentially harmful constituents (HPHC) testing demonstrated that the new and predicate tobacco product contain analytically equivalent quantities of total nicotine (↓13%), free nicotine (↓10%), cadmium (↓16%), B[a]P (↓13%), formaldehyde (↓6%), NNN (↓6%), NNK (↓5%), and acetaldehyde

(↑18%)[1]. The applicant provided nicotine dissolution testing that demonstrated that the dissolution profiles of the new and predicate tobacco products were statistically equivalent, suggesting that the nicotine release rates for the new and predicate tobacco products are similar despite the differences in the product characteristics. However, further information on the dissolution and HPHC testing methods (e.g., complete method protocols, validation report) was needed to fully evaluate the dissolution study and HPHC testing data and to determine whether the differences in product chemistry do not cause substantial differences in the nicotine released from the new and predicate tobacco products. A deficiency for this issue was communicated to the applicant. The applicant responded to the deficiency letter, referencing a tobacco product master file (TPMF), and its amendments, to address the deficiency. Chemistry found the response suitable to verify the nicotine dissolution and HPHC testing. Consequently, the differences in product characteristics (e.g.; difference in tobacco blends; presence of (b) (4) difference in pH adjusters) do not cause the new tobacco product to raise different questions of public health from a chemistry perspective.

4.2. ENGINEERING

An engineering review was completed by Michael Morschauser on December 19, 2020.

The engineering review concludes that the new tobacco product has different characteristics related to product engineering 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 difference:

- Increase in moisture (3%)

The increase in moisture (3%) in the new tobacco product is anticipated to be too small to affect the amount and rate of constituents released from the product. Therefore, the differences in characteristics between the new and predicate tobacco product do not cause the new tobacco product to raise different questions of public health from an engineering perspective.

4.3. MICROBIOLOGY

A microbiology review was completed by Almaris Alonso-Claudio on December 17, 2019.

The 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:

- 11-27% increases in total aerobic microbial counts (TAMC)
- 10% decrease in the amount of (b) (4) tobacco ((b) (4) vs. (b) (4) mg/g)
- 10% decrease in (b) (4), from the (b) (4) tobacco

[1] Chemistry conducted HPHC testing using a two one-sided t-tests approach.

- Change in duration of [redacted] vs. [redacted] days)
- Addition of a preservative, [redacted] mg/g), as an ingredient

The new and predicate tobacco products differ in amount of [redacted] tobacco component, duration of overall [redacted] process, and preservative levels, all of which could potentially affect microbial growth, which in turn could affect the microbial stability of the new tobacco product during storage. The applicant adequately addressed these concerns by providing stability testing data for the new and predicate tobacco products. However, the TAMC data of the new tobacco product showed increases (11-27%) at all time points during product storage compared to the predicate tobacco product. These increases in TAMC of the new tobacco product could be of concern because microbial-mediated reactions play a key role in the total tobacco-specific nitrosamines (TSNA) levels of the final tobacco product during product storage. However, the new tobacco product showed ≤4% changes in NNN, NNK, and total TSNAs compared to the predicate tobacco product at all storage timepoints. Therefore, the differences in characteristics between the new and predicate tobacco product 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 Juan Crespo-Barreto on December 23, 2019[2].

The 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:

- Addition of binder gums (↑ 21.00 mg/g)
- Addition of [redacted] (↓ [redacted] mg/g)
- Increase in moisture content (↑3-9% OV%)

The binders [redacted] and [redacted] are added to the new product, while not present in the predicate product. Based on the estimated average daily exposure, daily binder gum exposure associated with the new product use is below the oral toxicity-based reference values of intake established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Therefore, the addition of binders does not cause the new tobacco product to raise different questions of public health. The addition of [redacted] in the new product ([redacted] mg/g [redacted] (~[redacted] mg/g). The estimated [redacted] intake from the new product is calculated to be [redacted] µg /kg/day, which is below the available toxicity-based reference value for [redacted] intake established by EPA and WHO (chronic population adjusted dose 30 µg/kg/day). Therefore, the addition of [redacted] is unlikely to cause the new product to raise different questions of public health from the toxicological perspective. The reported increased moisture content in the new tobacco product is not associated

[2] On January 7, 2020, toxicology filed a memo to correct the sub-category in the toxicology review completed on December 23, 2019.

with analytically inequivalent increases in levels of TSNAs or any HPHC reported. Thus, increased moisture and water activity is unlikely to cause the new product to raise different questions of public health from the toxicological perspective. Therefore, the differences in characteristics between the new and predicate tobacco product do not cause the new tobacco product to raise different questions of public health from a toxicology perspective.

5. ENVIRONMENTAL DECISION

Environmental reviews were completed by Dilip Venugopal on December 12, 2019 and May 26, 2020.

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D., on January 2, 2020. The FONSI was supported by an environmental assessment prepared by FDA on January 2, 2020.

6. CONCLUSION AND RECOMMENDATION

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

- Tobacco blend:
  - ↓10% total tobacco
  - ↓11% (b) (4) tobacco
    - ↓13% (b) (4) [redacted]
  - ↓11% (b) (4) tobacco
    - ↓11% (b) (4) [redacted]
    - ↓11% (b) (4) [redacted]
  - ↓10% (b) (4) tobacco
  - Presence of (b) (4) tobacco (b) (4) mg/g)
  - ↓10% (b) (4) tobacco
- Presence of (b) (4) [redacted] mg/g)
- Replacement of (b) (4) [redacted] with (b) (4) [redacted] in container closure system
- Decrease in flavor ingredients (e.g., (b) (4) [redacted] [10%], (b) (4) [redacted] [9%])
- Presence of binder ingredients (b) (4) [redacted] mg/g (b) (4) [redacted] mg/g (b) (4) [redacted] m/g (b) (4) [redacted]; decrease in (b) (4) [redacted] [↓9%])
- Decrease in total nicotine (↓13%), free nicotine (↓10%), cadmium (↓16%), B[a]P (↓13%), NNN (↓6%), NNK (↓5%)
- Increase in acetaldehyde (↑18%)
- Increase in moisture (3%)
- 11-27% increases in total aerobic microbial counts (TAMC)
- 10% decrease in (b) (4) [redacted] from the (b) (4) [redacted] tobacco
- Change in duration of (b) (4) [redacted] vs. (b) (4) [redacted] days)

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health. The new and predicate tobacco

products have identical design specifications, except for a slight increase in moisture. The change in moisture is anticipated to be too small to affect the amount and rate of constituents released from the product. There are lower amounts of tobacco in the new tobacco product compared to the predicate tobacco product which may result in lower HPHCs. The applicant provided HPHC yields demonstrating that the new and predicate tobacco product contain analytically equivalent quantities of total nicotine, free nicotine, cadmium, B[a]P, formaldehyde, NNN, NNK, and acetaldehyde. Furthermore, the changes in the ingredients, as discussed by chemistry, microbiology, and toxicology, did not raise different questions of public health. Therefore, the differences in characteristics between the new and predicate product do not cause the new tobacco product to raise different questions of public health.

Where an applicant supports a showing of SE by comparing the new tobacco product to a tobacco product that FDA previously found SE, in order to issue an SE order, FDA must find that the new tobacco product is substantially equivalent to a tobacco product commercially marketed in the United States as of February 15, 2007 (see section 910(a)(2)(A)(i)(I) of the FD&CAct).

The predicate tobacco product in SE0015556 was previously determined to be substantially equivalent by FDA under SE0015104. The predicate tobacco product in SE0015104 was previously determined to be substantially equivalent by FDA under SE0014598. Comparison of the new tobacco product to the grandfathered tobacco product (Copenhagen Long Cut in SE0014598) reveals that the new tobacco product has the following differences in characteristics from Copenhagen Long Cut, the grandfathered tobacco product:

- Tobacco blend:
  - ↓10% total tobacco
  - ↓11% (b) (4) tobacco
    - ↓13% (b) (4) [redacted]
  - ↓11% (b) (4) tobacco
    - ↓11% (b) (4) [redacted]
    - ↓11% (b) (4) [redacted]
  - ↓10% (b) (4) tobacco
  - Presence of (b) (4) tobacco (b) (4) [redacted] mg/g)
  - ↓10% (b) (4) tobacco
- Presence of (b) (4) [redacted] mg/g)
- Decrease in flavor ingredients (e.g., (b) (4) [redacted] [10%], (b) (4) [redacted] [9%])
- Replacement of (b) (4) [redacted] with (b) (4) [redacted] in container closure system
- Presence of binder ingredients (b) (4) [redacted] mg/g (b) (4) [redacted] mg/g (b) (4) [redacted] m/g (b) (4) [redacted] decrease in (b) (4) [redacted] [↓9%]
- Changes in composition of (b) (4) tobacco resulting in addition of a preservative, (b) (4) [redacted] mg/g), addition of (b) (4) tobacco ((b) (4) mg/g) and removal of (b) (4) [redacted] (non-GRAS) to include GRAS (b) (4) [redacted] mg/g).
- Change in duration of (b) (4) [redacted] vs. (b) (4) [redacted])

The differences in characteristics listed above, other than the differences in the tobacco blend quantities, ingredients other than tobacco, changes in the TAMC and duration of the (b) (4) [redacted],

are the same differences in characteristics identified for the new and grandfathered tobacco product in SE0014598. Therefore, these differences do not cause the new tobacco product in SE0015556 to raise different questions of public health. Additionally, for the same reasons as discussed above, the differences in moisture and the container closure system between the new tobacco product in SE0015556 and the grandfathered tobacco product do not cause the new tobacco product to raise different questions of public health. Therefore, whether comparing the new tobacco product in SE0015556 to the predicate or grandfathered tobacco product, the new tobacco product does not raise different questions of public health.

The new tobacco product is currently in compliance with the FD&C Act. In addition, all of the scientific reviews conclude that the differences between the new and predicate tobacco product are such that the new tobacco product does not raise different questions of public health. I concur with these reviews and recommend that an SE order letter be issued.

FDA examined the environmental effects of finding this new tobacco product substantially equivalent and made a finding of no significant impact.

An SE order letter should be issued for the new tobacco product in SE0015556, as identified on the cover page of this review.