FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0015280

SE0015280: Copenhagen Long Cut Special Mint	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(D) (4) Cuts Per Inch (CPI)
Characterizing Flavor	Mint
Attributes of SE Report	
Applicant	U.S. Smokeless Tobacco Company LLC
Report Type	Regular
Product Category	Smokeless Tobacco Product
Product Sub-Category	Loose Moist Snuff
Recommendation	
Issue Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

Digitally signed by Gloria J. Kulesa -S
Date: 2020.04.27 11:29:40 -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: 2020.04.27 12:24:23 -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:

SE0015280: Copenhagen Long Cut Special Mint	
Product Name	Skoal Long Cut Mint
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b)(4) CPI
Characterizing Flavor	Mint

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

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On June 28, 2019, FDA received an SE Report from U.S. Smokeless Tobacco Company LLC. FDA issued an Acknowledgment letter to the applicant on July 8, 2019.

Product Name	SE Report	Amendments
Copenhagen Long Cut Special Mint	SE0015280	SE0015526

1.3. SCOPE OF REVIEW

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

2. REGULATORY REVIEW

A regulatory review was completed by Samuel Motto on July 8, 2019.

The 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 in the United States other than exclusively in test markets as of February 15, 2007). The OCE review dated July 28, 2019, 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.

OCE also 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 review dated April 3, 2020, concludes 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 August 12, 2019 and Delauren McCauley on March 17, 2020.

The 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:

- Total tobacco (↓12%): ↓12% (b) (4), ↓12% (b) (4) ↓12% (b) (4) (b) (4), ↓12% (b) (4)
- (b) (4) presence of (b) (4) mg/g); (b) (4) mg/g);
- Decrease in (b) (4) (↓9%), (b) (4) (↓12%), (b) (4) (↓70%), (b) (4) (↓72%)
- Presence of additives: (b) (4) (i.e., non-GRAS to GRAS), (b) (4) mg/g); (b) (4) mg/g)
- Absence of additives: (b) (4) (non-GRAS)
- Total nicotine (↓10%), B[a]P (↓10%), acetaldehyde (↓17%), NNN (↓13%)
- Free nicotine (↓21%) and NNK (↓18%)
- (b) (4) ingredients (↑55%): presence of (b) (4) flavor ((b) (4) mg/g) and absence of (b) (4) mg/g)
- pH Adjusters (↓9%): (b) (4) mg/g) and (b) (4) mg/g)
- Binders (total: (b) (4) mg/g): presence of (b) (4) mg/g), (b) (4) mg/g), and (b) (4) mg/g)

In SE0015280, the new and predicate tobacco products contain the same tobacco blend composition. However, the total tobacco amount and each tobacco blend type (e.g., (b) (4) is 12% lower in the new compared to the predicate tobacco product. Additionally, the difference in (b) (4) (i.e., (b) (4) between the new and predicate tobacco product is the presence of (b) (4) mg/g), (b) (4) mg/g), and (b) (4) (i.e., non-GRAS to GRAS). (b) (4) in mainstream smoke is known to emit higher levels of benzo[a]pyrene than other types of tobacco. However, (b) (4) is present in the new and predicate tobacco product at (b) (4) mg/g or 0.29% of the total tobacco weight. Lower amounts of tobacco in the new tobacco product compared to the predicate tobacco product may result in lower harmful and potentially harmful constituents (HPHCs). Therefore, the tobacco blend in the

new tobacco product is not expected to affect the characteristics of the new tobacco product compared to the predicate tobacco product and does not cause the new tobacco product to raise different questions of public health, from a chemistry perspective.

Furthermore, the new and predicate tobacco products contain the following differences in flavor ingredients: replacement of non-GRAS to GRAS (b) (4); (b) (4) (b) (4) (↓9%); replacement of [redacted] resulting in a ↑55% increase in (b) (4) (b) (4) (b) (4) (↑26%); presence of binders (i.e., [redacted] mg/g), [redacted] mg/g), [redacted] mg/g)); pH adjusters [redacted] (↓9%), [redacted] (↓9%)) and [redacted] (↓70%) and [redacted] mg/g)). In amendment SE0015526, the applicant addresses the toxicological impact of (b) (4) levels between the new and predicate tobacco product. However, chemistry defers this to toxicology for further evaluation. The applicant provided analytical data, demonstrating that the new compared to the predicate tobacco product contains analytically equivalent differences in total nicotine (↓10%), B[a]P (↓10%), acetaldehyde (↓17%), and NNN (↓13%). However, analytically non-equivalent differences between the new and predicate tobacco product includes free nicotine (↓21%) and NNK (↓18%). Since the HPHC levels decrease between the new and predicate tobacco product, it does not cause the new tobacco product to raise different questions of public health. From a chemistry perspective, the ingredients and HPHC levels between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

The applicant did not provide nicotine dissolution testing protocols or method validation reports in the first chemistry review cycle and therefore a deficiency was issued. In response to the dissolution deficiency, the applicant submitted amendment SE0015526, which included complete method protocols and validation reports for the nicotine and [redacted] dissolution testing data. In addition, the applicant provided scientific evidence to support that the differences in flavors, pH adjusters, and binders between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. The dissolution testing demonstrated that nicotine (f1= 2.3; f2= 86) and (b) (4) (f1= 12; f2= 59) dissolution profiles in the new and predicate tobacco products are statistically equivalent (f1 < 15; f2 > 50). As a result, the differences in product characteristics between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health, from a chemistry 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 chemistry perspective.

4.2. ENGINEERING

An engineering review was completed by Michael Morschauser on August 14, 2019.

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 differences:

- Increase in moisture (4%)

The new tobacco product has an increase in moisture (4%). The increase in moisture is anticipated to be too small to affect the amount and rate of constituents released from the product, and 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 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 David Craft on August 14, 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:

- A 12% reduction of [redacted]
- GRAS [redacted] replaces non-GRAS [redacted] in an identical amount (from [redacted])
- An addition of [redacted] mg/g) (from [redacted])
- An addition of [redacted] mg/g) (from [redacted])

The applicant provided stability testing data (pH, moisture, a_w, nitrate, nitrite, NNN, NNK, TSNA, TAMC, and TYMC) measured over the complete storage duration (beginning, middle, and end) of the new and predicate tobacco products. From a microbiology perspective, the differences between the new and predicate tobacco products are not of concern based on the ≤3% changes in pH, OV%, and a_w of the new tobacco product as compared to the predicate tobacco product. These changes were further substantiated by the supporting decreases in TAMC (≤48%) and TYMC (≤5 cfu/g) data when comparing the new to the predicate tobacco product. The NNN, NNK, and total TSNA content of the new tobacco product showed decreases (≤17%) when compared to the predicate tobacco product at the beginning, middle and end of product storage. In addition, the new tobacco product showed decreases in NNN (10%), NNK (17%) and total TSNA (10%) content over the complete storage duration.

In conclusion, evaluation of the complete stability data of the new and predicate tobacco products submitted by the applicant shows that 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 with regards to product microbiology.

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

A toxicology review was completed by Ryan Haskins on March 20, 2020.

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:

- (b) (4) and (b) (4) (GRAS) are added to the new tobacco product's
- [redacted] mg/g), [redacted] mg/g), [redacted] mg/g), [redacted] mg/g), and [redacted] mg/g) are added to the tobacco filler of the new tobacco product.
- TOST analysis indicates an inequivalent decrease in NNK levels (↓18)

(b) (4) and (b) (4) (GRAS) were added to the new tobacco product's [redacted] compared to the predicate tobacco product's [redacted]. The daily oral exposure to [redacted] in the [redacted] is estimated to be [redacted] µg/kg/day, which is below European Food Safety Agency (EFSA) tolerable daily intake (TDI) of 3 µg/kg/day. The (b) (4) (GRAS) added to the [redacted] has been determined to be GRAS by the FDA. While GRAS status is not applicable to tobacco products, that [redacted] are appropriate for use in food can inform their intended use in an oral tobacco product. Thus, the addition of (b) (4) and (b) (4) (GRAS) to the [redacted] does not cause the new tobacco product to raise different questions of public health from a toxicological perspective.

[redacted] are added to the tobacco filler of the new tobacco product compared to the predicate tobacco product. The active ingredient in the [redacted], is reported at approximately [redacted] mg/g in the new product and its daily oral exposure is estimated to be [redacted] mg/kg bw/day, which is below the Joint FAO/WHO Expert Committee on Food Additives (JECFA) acceptable daily intake (ADI) at 1.67 mg/kg/day. [redacted] derived from the [redacted] present in the new tobacco product is reported at approximately [redacted] mg/g and its daily oral exposure is estimated to be [redacted] mg/kg bw/day, which is below the JECFA ADI at 4 mg/kg bw/day. Regarding [redacted] potential permeation effect, current available information indicates that [redacted] products do not appear to lead to greater dependence or increased exposure to nicotine or carcinogens. The [redacted] added to the tobacco filler of the new tobacco product have all been determined to be GRAS by the FDA. In addition, the [redacted] added to the tobacco filler of the new tobacco product replaces a larger amount of a non-GRAS (b) (4). While GRAS status is not applicable to tobacco products, it may inform the toxicological review of compounds added to an oral tobacco product. Although [redacted] is added to the tobacco filler of the new tobacco product, total (b) (4) content is decreased in the new tobacco product compared to the predicate tobacco product. Taken together, the addition of these ingredients to the new tobacco product does

not cause the new tobacco product to raise different questions of public health from a toxicological perspective.

The applicant provided measurements for acetaldehyde, arsenic, benzo[a]pyrene, cadmium, crotonaldehyde, formaldehyde, NNK, and NNN for the new and predicate tobacco products. Of these HPHCs, NNK was analytically inequivalent, but it decreased in the new tobacco product, while the remaining HPHCs were analytically equivalent. Thus, the reported HPHC measurements do not cause the new tobacco product to raise different questions of public health from a toxicological perspective.

The applicant also adequately addressed Deficiency 2, issued in August 2019, related to the increased menthol content of the new tobacco 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 a toxicology perspective.

5. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on March 16, 2020. The FONSI was supported by an environmental assessment prepared by FDA on March 16, 2020.

6. CONCLUSION AND RECOMMENDATION

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

- Increase in moisture
- Decrease in total tobacco, including all blends, with a presence of [redacted]
- Decreases in total nicotine, B[a]P, acetaldehyde, NNN, NNK, and free nicotine
- Decrease in additives: [redacted]
- Presence of additives: [redacted]
- Absence of additives: (b) (4) (non-GRAS)
- [redacted] ingredients: increase in [redacted] due to the presence of [redacted]
- Decrease in pH Adjusters: [redacted]
- Binders: presence of [redacted]

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 machine settings and design specifications, except for a slight decrease in the moisture. The change in moisture is anticipated to be too small to affect the amount and rate of constituents released from the product. Therefore, the change in moisture does not cause the new

tobacco product to raise different questions of public health. Lower amounts of tobacco in the new tobacco product compared to the predicate tobacco product may result in lower harmful and potentially harmful constituents (HPHCs). The applicant provided measurements for acetaldehyde, arsenic, benzo[a]pyrene, cadmium, crotonaldehyde, formaldehyde, NNK, NNN, nicotine, and free nicotine for the new and predicate tobacco products. Of these HPHCs, NNK and free nicotine were analytically inequivalent, but the values decreased in the new tobacco product, while the remaining HPHCs were analytically equivalent. Therefore, the reported HPHC measurements and lower amounts of tobacco in the new tobacco product do not cause the new tobacco product to raise different questions of public health. Furthermore, the changes in the additives, as discussed by chemistry 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.

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

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 SE0015280, as identified on the cover page of this review.