FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0000544, SE0000545 and SE0005223

SE0000544: Skoal Pouches Smooth Mint	
Package Type	Plastic can and metal lid
Package Quantity	23.25 g
Portion Count	15 portions
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Mint
SE0000545: Skoal Pouches Straight	
Package Type	Plastic can and metal lid
Package Quantity	23.25 g
Portion Count	15 portions
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	None
SE0005223: Copenhagen Pouches Alaska and Hawaii, Overseas Military	
Package Type	Plastic can and lid
Package Quantity	23.25 g
Portion Count	15 portions
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	U.S. Smokeless Tobacco Company LLC
Report Type	Provisional
Product Category	Smokeless tobacco product
Product Sub-Category	Portioned, moist snuff
Recommendation	
Issue Substantially Equivalent (SE) orders.	

Technical Project Lead (TPL):

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Date: 2019.04.16 10:10:57 -04'00'

Shixia Feng, 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)

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Date: 2019.04.16 11:04:10 -04'00'

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

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1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted the following predicate tobacco products:

SE0000544: Skoal Pouches Smooth Mint	
Product Name	Skoal Pouches Mint
Package Type	Plastic can and metal lid
Package Quantity	23.25 g
Portion Count	15 portions
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Mint
SE0000545: Skoal Pouches Straight	
Product Name	Copenhagen Pouches
Package Type	Fiberboard can and metal lid
Package Quantity	23.25 g
Portion Count	15 portions
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	None
SE0005223: Copenhagen Pouches Alaska and Hawaii, Overseas Military	
Product Name	Copenhagen Pouches
Package Type	Fiberboard can and metal lid
Package Quantity	23.25 g
Portion Count	15 portions
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	None

The predicate tobacco products are portioned, moist snuff smokeless tobacco products manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 18, 2011, FDA received three Substantial Equivalence (SE) Reports from U.S. Smokeless Tobacco Company LLC (USSTC). FDA issued Acknowledgement letters to the applicant on October 14, 2011, for SE0000544 and SE0000545 and on December 26, 2012, for SE0005223. On November 4, 2011, and May 11, 2012, FDA received amendments correcting information in the SE reports. On December 27, 2012 (for SE0005223) and on January 2, 2013 (for SE0000544 and SE0000545), FDA issued Advice/Information (A/I) Request letters requesting additional information. In response, the applicant submitted amendments on January 25, 2013. On February 1, 2013 (for SE0000545), on May 29, 2013 (for all STNs), on May 30, 2013 (for SE0000544), and on July 19, 2014 (for SE0000544 and SE0000545), FDA received amendments correcting information in the SE reports. On November 10, 2014, FDA issued a Notification letter to inform the applicant that scientific review of the SE Reports would commence on December 26, 2014. On December 19, 2014, FDA received an amendment containing updates to the unique product information. On February 10, 2015, FDA received an amendment for SE0000544 and SE0000545 updating the tobacco ingredient listing. On November 25, 2015, FDA received an amendment for SE0000544 containing an update to the tobacco product name. On July 28, 2016, FDA issued an A/I letter requesting additional information. On August 5, 2016, FDA issued a correction letter for the July 28, 2016, A/I letter. On August 31, 2016, FDA issued an A/I letter requesting additional information. In response, the applicant submitted an amendment on October 28, 2016. On January 3, 2018, FDA issued a Preliminary Finding (PFind) letter requesting additional information. On January 12, 2018, FDA received an amendment containing a request for extension of time to FDA's January 3, 2018, PFind letter. On January 26, 2018, FDA issued an Extension Granted letter, extending the response date to January 15, 2019. On January 15, 2019, FDA received an amendment in response to the PFind letter dated January 3, 2018. On February 15, 2019, FDA emailed clarification questions to the applicant regarding the January 15, 2019, amendment. On February 21, 2019, FDA received an amendment containing responses to FDA's clarification question sent on February 15, 2019. On March 19, 2019, FDA received an amendment containing responses to a request made by the Office of Compliance and Enforcement for the characterizing flavor of the predicate tobacco products.

Product Name	SE Report	Amendments
Skoal Pouches Smooth Mint	SE0000544	SE0003914 SE0004481 SE0006758 SE0008729 SE0008758 SE0009336 SE0010808 SE0010900 SE0012694 SE0013733 SE0014468 SE0015062 SE0015091 SE0015127

Skoal Pouches Straight	SE0000545	SE0003916 SE0004482 SE0006759 SE0007037 SE0008732 SE0009326 SE0010809 SE0010901 SE0013733 SE0014468 SE0015062 SE0015091 SE0015127
Copenhagen Pouches Alaska and Hawaii, Overseas Military	SE0005223	SE0003856 SE0004415 SE0006724 SE0008676 SE0010810 SE0013733 SE0014468 SE0015062 SE0015127

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 Angela Brown on July 27, 2016, by Samuel Motto on August 5, 2016, and by Antonio Thornton on January 26, 2018.

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 as of February 15, 2007). The OCE reviews dated November 25, 2014 and March 22, 2019, 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. SCIENTIFIC REVIEW

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

4.1. CHEMISTRY

Chemistry reviews were completed by Jianping Gong on February 28, 2015 and January 4, 2017, and by Mimy Young on March 5, 2019.

The final chemistry review concludes that the new tobacco products have different characteristics related to product chemistry compared to the 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:

- Higher amount of (b) (4) tobacco (↑ 13-31% in SE0000544 and SE000545)
- Addition of (b) (4) mg/g (b) (4) tobacco
- Higher amount of (b) (4) tobacco (↑ 33% in SE0000544)
- Higher amount of (b) (4) tobacco (↑ 171% in SE0000545)
- Lower amount of (b) (4) tobacco (↓ 65% in SE0000544)
- Lower amount of (b) (4) tobacco (↓ 48% in SE0000545)
- Differences in flavor ingredients (SE0000544 and SE0000545)
  - SE0000544: higher amount of (b) (4) (↑370%) and addition of (b) (4) ((b) (4) mg/g)[1]
  - SE0000545: addition of (b) (4) ((b) (4) mg/g) and (b) (4) ((b) (4) mg/g)
- Differences in pH adjuster ingredients (SE0000544 and SE0000545)
  - SE0000544: removal of (b) (4) and (b) (4)
  - SE0000555: addition of (b) (4) and (b) (4)
- Replacement of fiberboard can with plastic can (SE0000545 and SE0005223)
- Lower levels of free nicotine (↓ 2-39%) and NNN (↓20-46%) in SE0000544 and SE0000545; nicotine (↓ 13%), NAT (↓52%), NAB (↓65%), acetaldehyde (↓34%), arsenic (↓29%), and cadmium (↓35%) in SE0000544
- Higher levels of nicotine (↑ 9-10% in SE0000545 and SE0005223); B[a]P (↑11%) and formaldehyde (↑88%) in SE0000544; NAT (↑ 10%) and NNK (↑ 28%) in SE0000545

All SE Reports contain (b) (4) mg/g (b) (4) tobacco that is 1% of the total tobacco blend and not expected to change the HPHC profile. In SE0000544, the new product contains 33% higher amount of (b) (4) tobacco that may contain higher levels of polycyclic aromatic hydrocarbons (PAHs from hardwood smoke) and nicotine. Also, in SE0000545, the new product contains 171% higher amount of (b) (4) tobacco that may contain higher levels of nicotine and tobacco-specific nitrosamines (TSNAs). However, the new products in SE0000544 and SE0000545 contain 65% lower amount of (b) (4) tobacco and 48% lower amount of (b) (4) tobacco, respectively. The applicant provided HPHC measurements, demonstrating that all SE Reports contain analytically equivalent or lower levels of nicotine, free nicotine, TSNAs (e.g., NNN, NNK, NAT, NAB) compared to the predicate or surrogate predicate products that does not cause the new products to raise different

[1] In SE0000544, (b) (4) ((b) (4) mg/g) is removed and (b) (4) ((b) (4) mg/g) is added.

questions of public health. However, in SE0000544, additional HPHC measurements demonstrated that the new product contains lower levels of HPHCs (e.g., acetaldehyde, arsenic, and cadmium), except for B[a]P (↑ 11%) and formaldehyde (↑ 88%) compared to the surrogate predicate product. The levels of B[a]P are determined to be analytically equivalent, but the levels of formaldehyde are not analytically equivalent. This issue was deferred to toxicology to determine whether the higher level of formaldehyde in the new product for SE0000544 raises different questions of public health.

Furthermore, in SE0000544 and SE0000545, the applicant submitted dissolution testing data as scientific evidence to support that the differences in portion thickness and other product design parameters (i.e., tobacco particle size and pouch permeability) between the new and predicate products do not cause the new products to raise different questions of public health. The dissolution testing is acceptable from a chemistry perspective and demonstrates that dissolution profiles of the new and corresponding predicate products are statistically equivalent ($f2 > 50$). Therefore, differences in product chemistry or product design do not cause substantial differences in the nicotine released from new and corresponding predicate products.

Moreover, in SE0000544 and SE0000545, the new products contain differences in pH adjuster and flavor ingredients. The difference (↓ 3%) in measured pH testing data is minor, therefore, the difference in pH adjuster does not cause the new products to raise different question of public health. SE0000544 and SE0000545 contain higher amount of (b) (4) compared to the corresponding predicate products. Additionally, SE0000544 contains (b) (4) (b) (4) and SE0000545 contains (b) (4) that is not present in the corresponding predicate products. The evaluation of toxicological impact of these differences were deferred to Toxicology.

Therefore, 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 Komal Ahuja on February 25, 2015, Tiffany Petty on January 3, 2017, and Ryan Andress on February 22, 2019.

For SE0000545 and SE0005223, the final engineering review did not identify any differences in characteristics between the new and corresponding predicate tobacco products that could cause the new tobacco products to raise different questions of public health from an engineering perspective.

For SE0000544, the final engineering review concludes that the new tobacco product has different characteristics related to product engineering compared to the corresponding 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 particle size: increase

- Moisture: 4% increase
- Pouch material basis weight: 76% increase
- Pouch material permeability: 150% increase
- Pouch material caliper: 318% increase

For SE0000544, there is difference in pouch materials between the new product and the predicate product, which includes a 76% increase in pouch material basis weight, a 318% increase in pouch material caliper, and a 150% increase in pouch material permeability. In addition, there is an increase in tobacco particle size. These differences may affect nicotine release rate. An evaluation of the nicotine dissolution data was deferred to the chemistry review. The moisture of the new product is 4% larger than the moisture of the predicate product. The increase in moisture in SE0000544 does not raise different questions of public health from an engineering perspective.

Therefore, 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 and engineering perspective.

4.3. TOXICOLOGY

Toxicology reviews were completed by Arianne Motter on October 16, 2015 and June 15, 2017, and by Guy Lagaud on March 11, 2019.

The final toxicology review concludes that the new tobacco products have different characteristics related to 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 (b) (4) tobacco
- Increase in (b) (4) tobacco (SE0000544)
- 88% increase in formaldehyde (SE0000544)
- Addition of (b) (4) (SE0000545)
- Increase in (b) (4) (SE0000544 and SE0000545)
- Addition of (b) (4)

To address the differences in tobacco blend, the applicant provided HPHC testing data. For SE0000544, increased (b) (4) tobacco could increase PAH levels. However, HPHC testing data indicates no statistical difference in B[a]P level in the new product compared with the surrogate predicate product. The HPHC data also indicated an 88% increased level in formaldehyde and 29-55% concomitant decreased levels in NNN, NNK, arsenic, cadmium, and acetaldehyde in the new tobacco product determined by the chemistry discipline to be analytically non-equivalent. The toxicology qualitatively evaluated whether these changes would be expected to increase the cancer risk of the new tobacco product compared to the surrogate predicate tobacco products. In addition, it was considered that the new product is a smokeless tobacco product, the route of exposure is oral, and the estimated total amount of formaldehyde increased in the new tobacco product in relatively low (µg/g) compared to the surrogate predicate tobacco product. It was also considered that formaldehyde is produced

endogenously at low levels, is present in the environment, and known in foods as a naturally occurring compound. Considering that this increase in formaldehyde in the new product is offset by the decreases of NNN, NNK, arsenic, cadmium, and acetaldehyde in the new product, toxicology concluded that the potentially increased cancer risk due to the increased formaldehyde is not likely greater than the decrease in cancer risk from NNN, NNK, arsenic, cadmium, and acetaldehyde that are decreased in the new tobacco product. For SE0000445, although not directly applicable to tobacco, the addition of (b) (4) is not expected to raise toxicological concern given that it has been considered by JECFA that this ingredient can be safely used in food without toxicological concern at current level of intake. For SE0000544, the first round of toxicology review noted that there was a replacement of (b) (4) ((b) (4) mg/g) with (b) (4) ((b) (4) mg/g). Although it was not clearly stated in the toxicology reviews, I do not have concern about the replacement of (b) (4) with a lower level of (b) (4) given the amount of this ingredient and the decreases in the abovementioned HPHC levels. Furthermore, the 1st round and 2nd round of toxicology reviews also evaluated the addition of (b) (4) (all SE Reports) and increases in (b) (4) (b) (4) (SE0000544 and SE0000545) and concluded that these do not raise toxicological concern at the stated use levels.

Therefore, 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 toxicology perspective.

4.4. MICOBIOLOGY

Microbiology reviews were completed by Norma Duran on March 5, 2015, and by Prashanthi Mulinti on December 16, 2016.

The final microbiology review concludes that the new tobacco products have different characteristics related to product microbiology 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 difference related to microbiology:

- Addition of the preservative (b) (4)

All of the new tobacco products contain (b) (4). The applicant submitted results from a 21-day microbiological challenge study of the new products which showed no background microflora in any of the control new products tested. There was also a decrease in the counts of the pathogenic *E.coli* and *Salmonella* species inoculated into the new products by day 8 of the study. The applicant did not submit any microbial counts or preservative levels measured over product storage time for the new or corresponding predicate products. However, the applicant adequately addressed this concern by providing data that showed relatively stable NNN, NNK and total TSNA levels from the start of fermentation to the end of new product storage time. The applicant also provided data to support the use of (b) (4) (b) (4) for effective inhibition of TSNA accumulation during fermentation process. In addition, the applicant provided information on the preventive initiatives taken to sanitize the processing equipment and prevent any growth of undesirable or nitrate reducing microorganisms. In addition to the (b) (4) as noted

in the final microbiology review, there is also a change in container closure system from fiberboard can to plastic can in SE0000545 and SE0005223. However, the stability data indicates that this change does not raise concern.

Therefore, 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.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act for these provisional SE Reports (SE0000544, SE0000545, and SE0005253) 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 predicate tobacco products:

- Higher amount of (b) (4) tobacco (↑ 13-31% in SE0000544 and SE000545)
- Addition of (b) (4) mg/g (b) (4) tobacco
- Higher amount of (b) (4) tobacco (↑ 33% in SE0000544)
- Higher amount of (b) (4) tobacco (↑ 171% in SE0000545)
- Lower amount of (b) (4) tobacco (↓ 65% in SE0000544)
- Lower amount of (b) (4) tobacco (↓ 48% in SE0000545)
- Differences in flavor ingredients (SE0000544 and SE0000545)
    - SE0000544: higher amount of (b) (4) (↑370%) and replacement of (b) (4) ((b) (4) mg/g) with (b) (4) ((b) (4) mg/g)
    - SE0000545: addition of (b) (4) ((b) (4) mg/g) and (b) (4) ((b) (4) mg/g)
- Differences in pH adjuster ingredients (SE0000544 and SE0000545)
    - SE0000544: removal of (b) (4) and (b) (4)
    - SE0000555: addition of (b) (4) and (b) (4)
- Replacement of fiberboard can with plastic can (SE0000545 and SE0005223)
- Lower levels of free nicotine (↓ 2-39%) and NNN (↓20-46%) in SE0000544 and SE0000545; nicotine (↓ 13%), NAT (↓52%), NAB (↓65%), acetaldehyde (↓34%), arsenic (↓29%), and cadmium (↓35%) in SE0000544
- Higher levels of nicotine (↑ 9-10% in SE0000545 and SE0005223); B[a]P (↑11%) and formaldehyde (↑88%) in SE0000544; NAT (↑ 10%) and NNK (↑ 28%) in SE0000545
- Tobacco particle size: increase (in SE0000544)
- Moisture: 4% increase (in SE0000544)
- Pouch material basis weight: 76% increase (in SE0000544)
- Pouch material permeability: 150% increase (in SE0000544)
- Pouch material caliper: 318% increase (in SE0000544)

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco products to raise different questions of public health. The new and corresponding predicate tobacco products have differences in the tobacco blend, but these do not raise different questions of public health based on the chemistry and toxicology reviews of the HPHCs data. Except for formaldehyde (88% increase) in SE0000544, all other measured HPHCs (nicotine, free nicotine, B[a]P, NNN, NNK, acetaldehyde, arsenic, and cadmium) in all of the new tobacco products are either lower or within the expected analytical variability compared to the corresponding predicate or surrogate predicate tobacco products. For formaldehyde in SE0000544, the toxicology review indicates that the estimated increase in formaldehyde exposure due to the use of the new tobacco product is small compared to other sources of exposure. Additionally, increase in formaldehyde is offset by the 29-55% decreases of NNN, NNK, arsenic, cadmium, and acetaldehyde. Therefore, the toxicology review concludes that the potentially increased cancer risk due to the increased formaldehyde is not likely greater than the decrease in cancer risk from the decreased NNN, NNK, arsenic, cadmium, and acetaldehyde, and therefore, does not raise different questions of public health for SE0000544. Furthermore, the differences in (b) (4) (all SE Reports) and in flavor ingredients (SE0000544 and SE0000545) do not raise concern at the levels used. For SE0000544 and SE0000545, the new products contain different pH adjusters compared to their corresponding predicate tobacco products; however, the measured pH data are similar. For SE0000544, although there are differences in product design parameters (tobacco particle size, pouch permeability, and portion thickness), the dissolution testing data showed similar nicotine release profiles between the new and predicate tobacco products, demonstrating differences in design parameters do not raise concerns. With regard to stability, the applicant has provided data to support the use of (b) (4) (b) (4) as a preservative added in all of the new tobacco products and a change in container closure system in SE0000545 and SE0005223. The data showed stable NNN, NNK, and total TSNA levels from the start of fermentation to the end of new product storage time. Therefore, 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.

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

In addition, all of the scientific reviews conclude that the differences between the new and corresponding predicate tobacco products are such that the new tobacco products do not raise different questions of public health. I concur with these reviews and recommend that SE order letters be issued.

Because the proposed action is issuing SE orders for the provisional SE Reports, 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.

SE order letters should be issued for the new tobacco products in SE0000544, SE0000545 and SE0005223, as identified on the cover page of this review.