FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0000443

SE0000443: Cope Long Cut Straight	
Package Type	Plastic Can and Metal Lid
Package Quantity	34.02 grams
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	Loose Moist Snuff
Recommendation	
Issue a Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

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Date: 2019.02.07 14:38:58 -05'00'

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: 2019.02.07 15:25:42 -05'00'

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:

SE0000443: Cope Long Cut Straight	
Product Name	Husky Long Cut Straight
Package Type	Plastic Can and Lid
Package Quantity	34.02 grams
Tobacco Cut Size[1]	(b) (4)
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 a Substantial Equivalence (SE) Report from U.S. Smokeless Tobacco Manufacturing Company, LLC on March 18, 2011. FDA issued an Acknowledgment letter on September 22, 2011. On November 4, 2011, FDA received an unsolicited amendment (SE0003934) containing the change of definition of "Long cut" in the Glossary. On May 11, 2012, FDA received unsolicited amendment (SE0004401) containing updated ingredients. FDA issued an Advice/Information Request (A/I) letter on December 15, 2012. On January 14 and 25, 2013, and May 28, 2013, FDA received applicant's response to the A/I letter (SE0005991, SE0006762, and SE0008618). On July 25, 2013, FDA received an unsolicited amendment (SE0009388) containing the correction of the target and range of Nerol. On February 10, 2015, FDA received an unsolicited amendment (SE0010881) containing an updated ingredient table. FDA issued a Notification letter on October 9, 2015. On November 20, 2015, FDA received an unsolicited amendment (SE0012677) containing updates to the original SE Report. On December 16, 2016, FDA received a solicited amendment (SE0013770) containing requested information for the conversion of "additional predicate products" to "surrogate products". FDA issued a Preliminary Finding (PFind) letter on January 19, 2017. On January 30, 2017, FDA received a response to the PFind letter (SE0013854). FDA issued an A/I letter on June 22, 2017. On July 5, 2017, FDA received a request (SE0014192) for time extension to respond the A/I letter. FDA issued the Extension Granted letter on July 25, 2017. On October 17, 2017, FDA received applicant's response to the A/I letter (SE0014379). FDA issued a PFind letter on March 26, 2018. On March 29, 2018, FDA received a request (SE0014599) for a time extension to respond the PFind letter. FDA issued an Extension Granted letter on April 11, 2018. On October 19, 2018, FDA received applicant's response to the PFind letter (SE0014904).

[1] Tobacco base is comprised of (b) (4) .

Product Name	SE Report	Amendments
Cope Long Cut Straight	SE0000443	SE0003934 SE0004401 SE0005991 SE0006762 SE0008618 SE0009388 SE0010881 SE0012677 SE0013770 SE0013854 SE0014192 SE0014379 SE0014599 SE0014904

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 Ella Yeargin on December 15, 2012, Jennifer German on December 17, 2012, Atasi Poddar on December 28, 2012, February 6, 2013, and February 27, 2013, and Pin Zhang on January 4, 2019.

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 in the United States other than exclusively in test markets as of February 15, 2007). The OCE review dated March 2, 2017, 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.

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 May 2, 2017, December 12, 2017, and December 6, 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 does not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Changes in tobacco blend
  - Addition ((b) (4) overall) of (b) (4)
  - 41% decrease in (b) (4)
  - 118% increase in (b) (4)
  - 44% decrease in (b) (4)
- Changes in the quantities of pH adjusting ingredients
- 7% decrease in nicotine
- 62% increase in free nicotine[2]
- 14% decrease in NNN
- 24% decrease in NNK
- Greater decrease (27% vs. 16%) in NNK content during product storage
- Changes in packaging ingredients
  - Metal vs. plastic lid
  - C1S paper vs. Pressure sensitive C1s paper for the side label

The increase (b) (4) tobacco could affect tobacco-specific nitrosamine (TSNA) amounts, however the decreases in NNN and NNK demonstrate that this tobacco change in the new tobacco product does not cause concern. The new tobacco product uses different packaging materials, including the changing to a pressure sensitive paper for the side label and a metal (vs. plastic) lid. The side label does not contact the consumable tobacco product and so no concerns are evident from this change. The metal lid, which does contact the consumable portion of the new tobacco product, contains (b) (4) all of which conform to requirements for either food contact substances or food additives. Although FDA food contact or food additive provisions do not apply to tobacco products, the smokeless tobacco product is consumed by the same route as food, and there is some related applicability. Since the packaging ingredients do conform to food provisions and the new tobacco product has similar exposure routes to food, the differences in packaging materials do not present apparent concerns. There is an increase in pH adjuster quantities, which may be responsible cause the higher amount of free nicotine in the new tobacco product, even though total nicotine is less. Nicotine release data show comparable nicotine release rates between the new and predicate tobacco products. Evaluation of the free nicotine increase is deferred to Behavioral and Clinical Pharmacology review.

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 chemistry perspective.

[2] Calculated from total nicotine and pH using Henderson-Hasselbalch equation.

4.2. ENGINEERING

Engineering reviews were completed by Komal Singh on April 24, 2017, and December 1, 2017. The final engineering review concludes that the new tobacco product has different characteristics related to product engineering compared to the predicate tobacco product, but the differences does not cause the new tobacco product to raise different questions of public health. The review identified the following difference:

- 1% increase in tobacco cut size

Tobacco cut size may alter the particle surface area and accessibility of saliva to tobacco surfaces, thereby affecting the amount and rate of constituents that are released from the product. As evaluated in the chemistry review, the applicant provided dissolution testing results of nicotine for the new and predicate products. Both new and predicate tobacco products have similar nicotine release profiles, demonstrating that the increase in tobacco cut size is not 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 an engineering perspective.

4.3. MICROBIOLOGY

Microbiology reviews were completed by Almaris Alonso on April 18, 2017, and December 18, 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 does not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Change in container-closure system (plastic can with metal lid)
- Addition of (b) (4) as a preservative
- Increase in NNK levels at the beginning of fermentation
- 26% and 32% respective decreases in NNN at the beginning and end of product storage
- 27% and 11% respective increases in NNK at the beginning and end of product storage
- 12% and 16% respective decreases in Total TSNAs at the beginning and end of product storage

(b) (4) is added as a preservative in the new tobacco product and should benefit reductions in microbial activity and lower TSNA levels. Stability studies show that the new tobacco product has higher NNK amounts at the beginning and end of product storage times, but it also has comparable offsetting decreases in NNN. Furthermore, total TSNAs are decreased at both the star and finish of storage for 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 from a microbiology perspective.

4.4. TOXICOLOGY

Toxicology reviews were completed by Carmine Leggett on May 16, 2017, December 21, 2017, and December 6, 2018.

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

- Decreases in NNN and NNK quantities

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. BEHAVIORAL AND CLINICAL PHARMACOLOGY

A behavioral and clinical pharmacology review was completed by Steven Meredith on December 22, 2017.

The behavioral and clinical pharmacology review concludes that the new tobacco product has different characteristics related to consumer use of the product and impact on exposure and behavior compared to the predicate tobacco product and that the SE Report lacks adequate evidence to demonstrate that the differences does not cause the new tobacco product to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. SE0000443 provides measured pH, nicotine, and calculated free nicotine values for the new and predicate products. The information you provided shows that free nicotine content at the measured pH is substantially higher in the new compared to the predicate product. You referenced published smokeless tobacco studies and stated these studies show use topography is the primary factor in nicotine absorption, not differences in product pH; however, only one of the published studies you cited examined the effects of smokeless pH on nicotine absorption, and this study (Pickworth et al., 2014) demonstrated smokeless tobacco pH is a primary determinant of nicotine absorption.

   Absorption of nicotine across oral mucosa is pH dependent. In its unionized state (pH above 6.5), nicotine is well-absorbed in the mouth, resulting in larger and more rapid increases in blood nicotine levels relative to nicotine in its ionized state. Thus, changes in free nicotine content may affect nicotine exposure and use behaviors. For example, increasing the free nicotine content in smokeless tobacco products may lead to

increased nicotine dependence. Decreasing free nicotine content may result in compensatory behaviors and greater exposure to toxins in experienced users. In inexperienced users, decreasing free nicotine levels may increase initiation. Provide adequate scientific evidence that these changes in free nicotine content do not cause the new products to raise different questions of public health. Such evidence could include behavioral or pharmacokinetic data from a clinical study examining nicotine exposure from the new and predicate products.

Therefore, the review concludes that there was inadequate information from a behavioral and clinical pharmacology perspective to determine that 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.

However, I conclude that the differences in pH, nicotine, and free nicotine do not cause the new tobacco product to raise different questions of public health based on the nicotine dissolution studies evaluated by chemistry.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act provisional SE Reports 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:

- Changes in tobacco blend
  - Addition (b) (4) overall) of (b) (4)
  - 41% decrease in (b) (4)
  - 118% increase in (b) (4)
  - 44% decrease in (b) (4)
- Changes in the quantities of pH adjusting ingredients
- 7% decrease in nicotine
- 62% calculated increase in free nicotine
- 14% decrease in NNN
- 24% decrease in NNK
- Greater decrease (27% vs. 16%) in NNK content during product storage.
- Changes in packaging ingredients
  - Metal vs. plastic lid
  - C1S paper vs. Pressure sensitive C1s paper for the side label
- (b) (4) increase in tobacco cut size
- Addition of (b) (4) as a preservative

- Increase in NNK levels at the beginning of fermentation
- 26% and 32% respective decreases in NNN at the beginning and end of product storage
- 27% and 11% respective increases in NNK at the beginning and end of product storage
- 12% and 16% respective decreases in Total TSNAs at the beginning and end of product storage

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health. The packaging of the new tobacco product is not a concern because it is made from ingredients that are approved food contact or food additive substances and the new tobacco product is used orally, similar to food. The increase in (b) (4) tobacco and addition of (b) (4) as a preservative could affect HPHC yields. However, neither of these changes is a concern as demonstrated by decreases in the carcinogens NNN and NNK. With respect to stability of the new tobacco product, there is an increase in NNK at both the beginning and end of product storage times; however, there are also comparable offsetting decreases in NNN and total TSNAs with respect to product storage. There is also a decrease in nicotine. Overall, there are favorable decreases in these HPHCs which support that the tobacco and non-tobacco ingredient differences of the new tobacco product do not cause concerns. The new tobacco product does have an increase in cut size, which affects the surface area available for interaction with saliva in the oral cavity, and a 62% calculated increase in free nicotine, which is readily absorbed across the oral mucosa into the circulatory system. However, dissolution testing shows that the new and predicate tobacco products have similar nicotine release profiles, demonstrating that the increase in tobacco cut size is not a concern. Nicotine only dissociates to free nicotine when in solution. Because the increase in free nicotine is calculated from pH and total nicotine and does not consider the amount of nicotine in solution, the dissolution release studies are a more accurate *in-vitro* determinant to assess the amount of free nicotine potential between the new and predicate tobacco products. Since the nicotine release rates are the same between the new and predicate tobacco products, then by extension the amount of free nicotine may be predicted to also be consistent between the products. Accordingly, the nicotine dissolution studies are adequately sufficient to resolve the behavioral and clinical pharmacology deficiency and the calculated increase in free nicotine does not affect the determination of substantial equivalence. Therefore, the differences in characteristics between the new and predicate 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 they are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007).

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.

An SE order letter should be issued for the new tobacco product in SE0000443, as identified on the cover page of this review.