FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0005908

SE0005908: Grizzly Fine Cut Natural	
Package Type	Plastic Can and Metal Lid
Package Quantity	34 grams
Tobacco Cut Size	(b) (4)
Characterizing Flavor	None
Attributes of SE Report	
Applicant	American Snuff Company
Report Type	Provisional
Product Category	Smokeless Tobacco Product
Product Sub-Category	Loose, moist snuff
Recommendation	
Issue Substantially Equivalent (SE) orders.	

Technical Project Lead (TPL):

Digitally signed by Charles Feng -S
Date: 2019.08.19 12:18:30 -04'00'

Charles 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)

Digitally signed by Matthew R. Holman -S
Date: 2019.08.20 15:28:52 -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:

SE0005908: Grizzly Fine Cut Natural	
Product Name	Grizzly Premium Natural Fine Cut
Package Type	Plastic can and Plastic Lid
Package Quantity	34 grams
Tobacco Cut Size	(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 the SE Report on March 22, 2011. On February 14, 2013, FDA completed a Public Health Impact (PHI) review for this SE Report. FDA assigned SE0005908 to PHI Tier 1. FDA issued Acknowledgement and Advice/Information Request (A/I) letters on March 14, 2013. On March 21, 2013, FDA received the applicant's 30-day extension request (SE0007894) to collect the information to response to the A/I letter. On April 1, April 5, April 9, and April 11, 2013, FDA conducted teleconferences to discuss the applicant's timeline and proposal to amend the SE Report in response to the A/I letter. On April 11, 2013, FDA received the applicant's timeline and proposal to amend the SE Report (SE0008212). FDA issued an Extension Response letter on April 17, 2013, requesting the applicant submit a complete response to the A/I letter and any additional information prior to the start of scientific review. FDA issued a PHI A/I letter on May 10, 2013. On June 7, 2013, FDA received the applicant's response to the PHI A/I letter (SE0008918). On August 26, 2015, FDA conducted a detailed review of the product composition information in the amendment and reassigned the SE Report to PHI Tier 2. FDA issued a Notification letter on September 15, 2015[1], indicating that scientific review was expected to begin on October 30, 2015. On October 29, 2015, FDA received an amendment containing a revised SE report (SE0012580). FDA issued a Preliminary Finding (PFind) letter on March 2, 2016. On March 31, 2016, FDA received the applicant's response to the Pfind letter, which included the applicant's request for a claim of categorical exclusion (SE0013289). On June 7, 2016, FDA received an amendment containing corrected HPHC data for the predicate tobacco product (SE0013413). FDA issued a Scientific A/I letter on August 15, 2016. On August 24, 2016, FDA received the applicant's 8-month extension request (SE0013656) to conduct stability testing needed in response to the A/I letter. On August 30, 2019, FDA issued an Extension Granted letter with a response due date of June 14, 2017. On June 13, 2017, FDA received the

[1] A Notification letter was email to the applicant on September11, 2015, the letter identified the tobacco product as "Grizzly Premium Natural Snuff Pouches" with a scientific start date of October 26, 2015. On September 15, 2015, a Notification letter "Grizzly Fine Cut Natural" with a scientific start date of October 30, 2015 was mailed to the applicant.

applicant's response to the A/I letter (SE0014146). FDA issued a PFind letter on August 28, 2017[2]. On September 5, 2017, FDA received the applicant's 24-month extension request (SE0014306) to conduct a clinical study needed in response to deficiency #9 in the PFind letter. On September 26, 2017, FDA issued an Extension Granted letter with a response due date of May 24, 2019. On May 22, 2019, FDA received the applicant's response to the PFind letter (SE0015241).

Product Name	SE Report	Amendments
Grizzly Fine Cut Natural	SE0005908	SE0007894 SE0008212 SE0008918 SE0012580 SE0013289 SE0013413 SE0013656 SE0014146 SE0014306 SE0015241

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 Marcella White on March 14, 2013.

The review concludes that the SE Report is not administratively complete because the following information was not included in the SE Report:

1. Unique identification of the new and predicate tobacco products
2. Heating source of the new and predicate tobacco products
3. Other features
4. Environmental assessment

This information was provided during the scientific review process. Therefore, the SE Report is administratively complete.

[2] A Correction letter was issued on August 31, 2017. The letter was not applicable to SE0005908; instead it removed a deficiency pertinent to (b) (4)

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 May 5, 2016[3], 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 Jianping Gong on July 5, 2016[4], Lida Oum on August 3, 2017, and Abdur-Rafay Shareef on July 11, 2019.

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:

- 4% increase in (b) (4) tobacco
- 5% increase in (b) (4) tobacco
- 3% increase in (b) (4) tobacco
- 20% decrease in (b) (4)
- 23% increase in cadmium
- 19% decrease in B[a]P
- 85% decrease in acetaldehyde
- 27% increase in total nicotine
- 93% increase in free nicotine

The applicant provided tobacco blend and ingredients other than tobacco information. Minor changes were made to the tobacco blend, and the net difference between the new and predicate tobacco products was increased by (b) mg/g (5%). (b) (4) tobacco increased by (b) mg/g (5%), (b) mg/g (4%), and (b) mg/g (3%), respectively. The higher tobacco quantity was paired with a concomitant decrease in (b) (4) (b) mg/g (20%). The applicant provided HPHC yields to support the described changes. Using a two-one-sided t-

[3] An addendum review was completed on July 31, 2019 to clarify that the characterizing flavor of the predicate tobacco product is "None". The addendum review does not change the conclusion of the initial grandfather determination dated May 5, 2016.
[4] An addendum was completed on August 16, 2017, clarifying the deficiencies to convey to the applicant.

test, the following HPHCs were not found as equivalent in the new tobacco product compared to the predicate tobacco product, and were deferred to toxicology for health evaluation:

- higher cadmium (↑ 23%)
- lower B[a]P (↓ 19%)
- lower acetaldehyde (↓ 85%)

The following yields were determined to be equivalent in the new tobacco product compared to the predicate tobacco product:

- NNN yields decreased (↓ 12%)
- NNK yields decreased (↓ 7%)
- Formaldehyde yields decreased (↓ 11%)
- Arsenic mean values were numerically identical

In support of the submitted HPHC yields the applicant provided sufficient information to evaluate data quality, including quantitative test protocols, testing laboratory and accreditation, manufacture and testing dates, replicates, standard deviation, and raw data for HPHC yields. Furthermore, the applicant submitted dissolution data comparing nicotine or calculated free nicotine in the new tobacco product compared to the predicate tobacco product based on a Center for Drug Evaluation and Research (CDER) guidance. Careful evaluation of the submitted methods and data revealed some deviations from the CDER guidance without justification; however, at this time, no further information is needed since clinical data was submitted to support the applicant's claims that the new tobacco product does not raise different questions of public health compared to the predicate tobacco product. The clinical data is evaluated by Behavioral and Clinical Branch (BCP).

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

Engineering reviews were completed by Erdit Gremi on July 20, 2016, and Jim Melchiors on July 27, 2017, and July 2, 2019.

The final engineering review did not identify any differences in characteristics between the new and predicate tobacco product that could cause the new tobacco product to raise different questions of public health from an engineering 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 related to product engineering.

4.3. MICROBIOLOGY

Microbiology reviews were completed by Almaris Alonso on July 5, 2016 and David Craft on July 31, 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:

- Substantial increase in total TSNAs, NNN, NNK, total yeast and mold counts (TYMC) ((b) (4) only), and nitrite ((b) (4) only) at each time point tested over a (b) (4) storage period
- Substantial decrease in total aerobic microbial counts (TAMC) at each time point tested and nitrite ((b) (4) only) over a (b) (4) storage period

The applicant submitted microbial stability testing data over product storage time (b) (4) The microbial stability data included pH, aw, moisture, total TSNAs, NNN, NNK, nitrate, nitrite, TAMC and TYMC for each new and corresponding predicate tobacco product. Increases in TSNAs, NNN, NNK, and nitrite in the new tobacco product compared to the predicate tobacco product raised concerns from a microbiology perspective. However, when the total TSNA, NNN, NNK and nitrite content of the new tobacco product was compared from the beginning to the end of the product storage time, there were decreases in the levels of all these HPHCs. The decreases in TSNA, NNN, NNK and nitrite levels of the new tobacco product over product storage time addresses our concern regarding the variation in these levels between the new and predicate tobacco products.

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 Ying Bryant on July 13, 2106 and August 10, 2017, and by Cissy Li on July 15, 2019.

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 do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Cadmium was increased in the new product compared to the predicate product while acetaldehyde and B[a]P were decreased

The applicant showed that there were no or minor changes in product design, tobacco blend, or ingredients in the new product compared to the predicate tobacco product. The applicant reported increased levels and large batch-to-batch variability of cadmium in the new product, which may be attributable to agricultural variability. Considering this, the applicant's conservatively calculated chronic daily intakes (CDIs) for the new and predicate products were compared to the EPA's oral reference doses (RfDs) for cadmium to inform the toxicology evaluation. The CDIs for both products were 5-10 times lower than the EPA RfDs for cadmium,

suggesting that the absolute amounts of cadmium in the new and predicate tobacco products are unlikely to cause noncancer toxicity in the product users and therefore the cadmium increase in the new product is unlikely to cause noncancer toxicity. Since cadmium is not shown to be carcinogenic by the oral route, the increased cadmium is also unlikely to cause any changes in cancer risk. Therefore, the cadmium increase is unlikely to cause the new 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 a toxicology perspective.

4.5. BEHAVIORAL AND CLINICAL PHARMACOLOGY

Behavioral and clinical pharmacology reviews were completed by Colin Cunningham on August 8, 2017 and Babita Das on July 8, 2019.

The final 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, but the differences do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- 3% increase in average pH from the predicate to the new product
- 27% increase in average nicotine content (mg/g) from the predicate to the new product
- 93% increase in free nicotine content (mg/g) from the predicate to the new product

BCP identified increases in pH and total nicotine content, resulting in a 93% increase in the calculated free nicotine content. To address FDA's concerns that increased free nicotine may impact nicotine exposure and use behaviors, the applicant provided clinical data from a single-blind, multi-center, randomized, two-way crossover clinical study. The product use data included number of (b) (4) (b) (4) and (b) (4) from *ad libitum* (*ad lib*) use. Nicotine pharmacokinetic (PK) parameters included Area Under Curve ($AUC_{nic0240}$), maximum plasma nicotine concentration (C_{max}), and time at which maximum plasma nicotine concentration occurred (T_{max}). The results showed that mean values of all product use data did not differ between the new and predicate tobacco products, and mean $AUC_{nic0-240}$ and C_{max} were significantly lower for the new tobacco products while T_{max} remained the same. In addition, mean plasma cotinine concentration during the *ad lib* use was significantly lower for the new tobacco product as well. These data showed that despite a 93% increase in free nicotine content, the new product does not increase use behaviors, nicotine exposure, or plasma nicotine concentrations in adult moist snuff users.

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 behavioral and clinical pharmacology perspective.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of an SE order under section 910(a) of the FD&C Act for this provisional SE Report (SE0005908) 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 product:

- 4% increase in (b) (4) tobacco
- 5% increase in (b) (4) tobacco
- 3% increase in (b) (4) tobacco
- 20% decrease in (b) (4)
- 23% increase in cadmium
- 19% decrease in B[a]P
- 85% decrease in acetaldehyde
- 3% increase in average pH
- 27% increase in total nicotine
- 93% increase in free nicotine
- Substantial increase in total TSNAs, NNN, NNK, TYMC (b) (4) only), and nitrite (b) (4) only) at each time point tested over a (b) (4) storage period
- Substantial decrease in TAMC at each time point tested and nitrite (b) (4) only) over a (b) (4) storage period

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 differences in the tobacco blend and other ingredients, which may affect HPHC levels. However, except for a 23% increase in cadmium, the HPHC testing data showed decreases in acetaldehyde and B[a]P, and analytically equivalent levels of NNK, NNN, formaldehyde, and arsenic. The toxicology review indicates that cadmium is not shown to be carcinogenic by the oral route, and the calculated CDIs for the new and predicate tobacco products were lower than the EPA's reference doses for oral exposure to cadmium, suggesting the cadmium level in the new tobacco product is unlikely to cause noncancer toxicity for users of the new tobacco product. The decreased levels in acetaldehyde and B[a]P and analytically equivalent levels of NNK, NNN, formaldehyde, and arsenic do not increase the toxicity of the new tobacco product. Furthermore, despite a 93% increase in the calculated free nicotine due to the increases in pH and total nicotine content, BCP's review of the applicant's clinical data concludes that the new product does not change use behaviors, or increase nicotine exposure or plasma nicotine concentrations in adult users of the new tobacco product. Finally, the stability data showed that there were decreases in TSNAs, NNN, NNK and nitrite in the new tobacco product from the beginning to the end of the storage time, indicating the new product was stable over the storage time. 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.

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).

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 SE0005908, as identified on the cover page of this review.