FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0004824

SE0004824: Red Seal Fine Cut Natural	
Package Type	Plastic Can and Metal Lid
Package Quantity	42.53 g
Tobacco Cut Size	Not Provided[1]
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	U.S. Smokeless Tobacco Company LLC
Report Type	Regular
Product Category	Smokeless Tobacco
Product Sub-Category	Loose Moist Snuff
Recommendation	
Issue a Substantially Equivalent (SE) order.	

[1] The applicant did not provide a target value for the tobacco cut size for the new tobacco product; however, they provided information on the manufacturing steps, including the tobacco blend composition, machine cutter setting, the number of cuts, the sieve mesh, and the milling: tobacco blend composition of (b) (4) [redacted] The applicant stated that these tobacco cutting parameters are identical between the new and predicate tobacco products. In this case, FDA determined that no additional information regarding tobacco cut size was necessary to compare the new and predicate tobacco products.

Technical Project Lead (TPL):

Digitally signed by Matthew J. Walters -S
Date: 2019.03.29 09:07:35 -04'00'

Matthew J. Walters, Ph.D., MPH
CDR, U.S. Public Health Service
Deputy Director
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: 2019.03.29 09:09:25 -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:

SE0004824: Red Seal Fine Cut Natural	
Product Name	Red Seal Fine Cut Natural (2007)
Package Type	Plastic Can and Lid
Package Quantity	42.53 g
Tobacco Cut Size	Not Provided[2]
Characterizing Flavor	None

The predicate tobacco product is a loose moist snuff smokeless tobacco product manufactured by U.S. Smokeless Tobacco Company LLC.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On August 8, 2012, FDA received the Substantially Equivalent (SE) Report from Altria Client Services Inc. (ALCS) on behalf of U.S Smokeless Tobacco Company LLC (USSTC). On August 30, 2012, FDA received an unsolicited amendment (SE0004869) containing reference files which were inadvertently omitted from the original SE Report. FDA issued an Acknowledgment letter to the applicant on September 7, 2012. On December 28, 2012, FDA issued an Advice/Information Request (A/I) letter, requesting additional product information for the new and predicate tobacco products, a statement of compliance with Section 907 of the Federal Food, Drug and Cosmetic (FD&C) Act, and an environmental assessment . On January 24, 2013, FDA received the response (SE0007946) to the December 28, 2012 A/I letter. On April 3, 2013, FDA conducted a telecon to request the applicant to provide packaging type and size/weight for the new and predicate tobacco products. On April 5, 2013, FDA received the response (SE0008172) to the April 3, 2013 information request. FDA issued a Notification letter on April 30, 2013, indicating scientific review was expected to begin on June 14, 2013. On May 29, 2013, FDA received an amendment (SE0008711) containing an Environmental Assessment (EA). On June 13, 2013, FDA received an amendment (SE0008994) containing a correction to the Ingredients Comparison section of the original submission. FDA issued an A/I letter on December 30, 2013. On January 27, 2014, FDA received an amendment (SE0010130), requesting for time extension of 45-days to provide responses to the December 30, 2013 A/I letter. FDA issued an Extension Response letter, on February 4, 2014, requesting additional information in order to adequately assess and respond to the extension request. On February 7, 2014, FDA received the response (SE0010172) to the February 4, 2014 Extension Response letter. Subsequently, on February 14, 2014, FDA issued an Extension Granted letter with an extended response due date of April 14, 2014. On April 11, 2014, FDA received responses (SE0010382 and SE0010396) to the December 30, 2013, A/I letter. On February 10, 2015, FDA received an unsolicited amendment (SE0010905) containing a correction to the Ingredients

[2] The applicant did not provide a target value for the tobacco cut size for the predicate tobacco product; however, they stated that the following tobacco cutting parameters are identical between the new and predicate tobacco products: tobacco blend composition, machine cutter setting, the number of cuts, the sieve mesh, and the milling. In this case, FDA determined that no additional information regarding tobacco cut size was necessary to compare the new and predicate tobacco products.

Comparison section of the original SE Report. FDA issued a Preliminary Finding (PFind) letter on September 6, 2016. On September 13, 2016, FDA was contacted by the applicant requesting clarification on one of the deficiencies in the September 6, 2016 PFind letter. On September 21, 2016, FDA contacted the applicant via email to provide a response to their clarification question. On October 5, 2016, FDA received a response (SE0013719) to the September 6, 2016 PFind letter. On August 25, 2017, FDA received an unsolicited amendment (SE0014272) containing a corrected value in the ingredient table for the predicate tobacco product. Although FDA received this amendment after the response due date, the technical project lead (TPL) conducted a review of the amendment in conjunction with the TPL's review of all information submitted by the applicant as review of this amendment (received in August 2017) does not further delay FDA's continued review of this SE Report. The TPL determined that the August 25, 2017, amendment does not alter the conclusions of the previously finalized final scientific reviews because the amendment corrected an amount of (b) (4), an ingredient, in the predicate tobacco product. The information previously reported that this ingredient was in the predicate tobacco product at (b) (4) mg/g, and the corrected information indicated that this ingredient is in the predicate tobacco product in amounts of (b) (4) mg/g. This difference does not alter the conclusions of the finalized scientific reviews. FDA issued a PFind letter regarding environmental information requests on November 24, 2017. On December 21, 2017, FDA received the response (SE0014438) to the November 24, 2017 PFind letter. On March 6, 2018, a telecon was held requesting the applicant to submit the characterizing flavors for the new and predicate tobacco products. Subsequently, on March 6, 2018, FDA received an amendment (SE0014567) stating that neither the new nor predicate tobacco products have a characterizing flavor. The TPL determined that the March 6, 2018, amendment does not alter the conclusions of the final scientific reviews, as the applicant was only clarifying which tobacco products contained a characterizing flavor and which tobacco products did not which was previously captured in the scientific reviews.

Product Name	SE Report	Amendments
Red Seal Fine Cut Natural	SE0004824	SE0004869 SE0007946 SE0008172 SE0008711 SE0008994 SE0010130 SE0010172 SE0010382 SE0010396 SE0010905 SE0013719 SE0014272 SE0014438 SE0014567

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 Atasi Poddar on September 7, 2012, December 28, 2012, and April 4, 2013; Sara Hernandez on August 22, 2017; and Maria Suarez on April 4, 2018. The final review concludes that the SE Report is administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed 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 a test market as of February 15, 2007). The OCE reviews dated May 31, 2013 conclude 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.[3]

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), as required by section 905(j)(1)(A)(i) of the FD&C Act. The OCE reviews dated May 31, 2013, April 9, 2018, October 29, 2018, and March 8, 2019, 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 Katherine Lovejoy on October 3, 2013 and June 26, 2014, and by Robert Gahl on November 21, 2016.[4]

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:

- Different container closure system plastic can with a metal lid instead of a plastic can with a plastic lid
- A metal lid coated with (b) (4) is used instead of a plastic lid

[3] An addendum review was completed on March 14, 2018, 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 31, 2013.

[4] An addendum review dated September 21, 2017, updated and corrected the final chemistry review dated November 21, 2016. The addendum review concluded that the deficiency recommended for SE0004824 in the final chemistry review did not apply as the applicant had sufficiently demonstrated the information was not needed.

- A 1% decrease in the total amount of tobacco
- A 2% decrease in the amount of (b) (4) ((b) (4) mg/g), (b) (4) ((b) (4) mg/g), and (b) (4) tobacco ((b) (4) mg/g)
- An addition of (b) (4) mg/g of (b) (4) tobacco and a 10% increase in the amount of (b) (4) tobacco
- A 27%, 14%, and 17% decrease in the amount of NNN (3.77 µg/g), NNK (1.16µg/g), and total TSNA (9.34 µg/g), respectively
- A 3% increase in total nicotine (b) (4) mg/g) and a 33% decrease in free base nicotine ((b) (4) mg/g)
- A decrease in the product pH in the new tobacco product (b) (4)) compared to the predicate tobacco product ((b) (4))
- Addition of the preservative (b) (4)
- (b) (4) is used in the new tobacco product instead of (b) (4), a complex and proprietary flavor ingredient, used in the predicate tobacco product
- (b) (4) is used in the new tobacco product instead of (b) (4), a complex and proprietary flavor ingredient, used in the predicate tobacco product
- A 20% decrease in (b) (4)

The applicant provided information about the tobacco blend, ingredients added to tobacco, the product pH, and nicotine levels for the new and predicate tobacco products. The new and predicate tobacco products have the same tobacco varieties with minor differences in the relative quantities. There is a 1% decrease in the total amount of tobacco in the new tobacco product ((b) (4) mg/g) compared to the predicate tobacco product (b) (4) mg/g). There is a (b) (4) mg/g addition of (b) (4) tobacco, and a 2% decrease in (b) (4), (b) (4), and (b) (4) tobacco in the new tobacco product compared to the predicate tobacco product. The applicant also reported differences greater than 5% in the quantity of four ingredients added to tobacco ((b) (4), , (b) (4), (b) (4), and (b) (4)); however, these ingredients were present at less than (b) (4) mg/g in the new tobacco product and are unlikely to cause the new tobacco product to raise different questions of public health. Additionally, there was no difference in quantity between (b) (4) and (b) (4) and between (b) (4) and (b) (4) (b) (4). Although FDA has not established that GRAS status for substances used in foods is applicable for smokeless tobacco products, in this case, the GRAS designation may be informative for an adequate toxicological evaluation (see section 4.4 below) of the new tobacco product as compared to the predicate tobacco product. The applicant used validated and accurate methods to measure the product pH and levels of nicotine, NNN, NNK, and total TSNAs for a surrogate new tobacco product and the predicate tobacco product. As such, the applicant provided sufficient information in this case to demonstrate that data from the surrogate new tobacco product can be extrapolated to the new tobacco product. The new tobacco product has decreases of 27%, 14%, and 17% in the amount of NNN (3.77 µg/g), NNK (1.16 µg/g), and total TSNAs (9.34 µg/g), respectively, compared to the predicate tobacco product. The product pH of the new tobacco product is lower ((b) (4)) than the predicate tobacco product (b) (4)). The new tobacco product has a 3% increase in the amount of total nicotine ((b) (4) mg/g) compared to the predicate tobacco product but has a 33% decrease in the amount of free nicotine ((b) (4) mg/g). The decrease in free nicotine is expected to result in less nicotine uptake when used by a consumer. In this case, the decrease in HPHCs and pH, do not cause the new tobacco product to raise different questions of public health. 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.

4.2. ENGINEERING

Engineering reviews were completed by Christian Coyle on September 30, 2013, Christopher Brown on June 26, 2014 and by Julie Morabito on November 16, 2016.

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

- A 1% increase in final tobacco moisture
- Different container closure system: plastic can with a metal lid instead of a plastic can with a plastic lid

The applicant provided test protocols, quantitative acceptance criteria, and data sets for the surrogate new tobacco product and the predicate tobacco product and provided sufficient information to demonstrate that data from the surrogate new tobacco product can be extrapolated to the new tobacco product. The test data provided by the applicant demonstrates that the final tobacco moisture target specifications have been met for the surrogate new tobacco product. The applicant did not provide a target value for the tobacco cut size for the new and predicate tobacco products; however, they stated that the following tobacco cutting parameters are identical between the new and predicate tobacco products: tobacco blend composition, machine cutter setting, the number of cuts, the sieve mesh, and the milling. In this case, FDA determined that no additional information regarding tobacco cut size was necessary to compare the surrogate new tobacco product and predicate tobacco product. Therefore, the applicant adequately demonstrated that it is unlikely that any difference would exist between the tobacco cut size of the new and predicate tobacco products. The applicant submitted annotated illustrations of the packaging, material information, and a side-by-side comparison of the packaging for the new and predicate tobacco products. The new tobacco product uses a metal lid as part of the container closure system, while the predicate tobacco product uses a plastic lid. The container closure system differences 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 as the product design parameters were not affected by this change when compared between the new and predicate 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 an engineering perspective.

4.3. MICROBIOLOGY

Microbiology reviews were completed by Norma Duran on November 12, 2013, Shanil Haugen on June 11, 2014, and by Prashanthi Mulinti on November 16, 2016.

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:

- Different container closure system: plastic can with a metal lid instead of a plastic can with a plastic lid
- Addition of the preservative (b) (4)

Although differences in container closure system materials might result in different moisture levels (and thus different levels of bacterial growth), the applicant demonstrated that pH, water activity, and moisture content has limited variability over the storage time; thus, the change in container closure system materials do not cause the new tobacco product to raise different questions of public health. The applicant also demonstrated that the addition of the preservative (b) (4) resulted in consistent levels of (b) (4), NNN, NNK, and total TSNAs over time. 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 Hans Rosenfeldt on December 24, 2013, Mary Kushman on July 28, 2016 and by Wanyoike Kang'ethe on November 28, 2016.

The final toxicology review concludes that the new tobacco product has different characteristics related to product toxicity 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 metal lid coated with (b) (4) is used instead of a plastic lid
- Addition of the preservative (b) (4)
- (b) (4) is used instead of (b) (4), a complex and proprietary flavor ingredient
- (b) (4) is used instead of (b) (4), a complex and proprietary flavor ingredient

The applicant provided information regarding the composition of (b) (4) coated on the metal lid in the new tobacco product and demonstrated that the components did not transfer or undergo any physical or chemical changes that could impact the characteristics of the new tobacco product when compared to the predicate tobacco product. Additionally, the applicant has provided sufficient scientific evidence and rationale to explain why the inclusion of the preservative (b) (4) at levels that are predicted to exceed the average daily intake (ADI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), (b) (4) mg/kg/day) does not raise toxicological concerns when compared between the new and predicate tobacco products. The applicant explained that determination of JECFA's ADI had primarily considered (b) (4) toxic effects on thyroid physiology in the rat model, which is overly predictive of the risk in humans. This is within the daily exposure predicted for consumers of one can (b) (4) g) of the new tobacco product per day and does not cause the new tobacco product to raise different questions of public health as compared to the predicate

tobacco product. The applicant also explained that addition of (b) (4) was intended to (b) (4) the growth of endogenous (b) (4)-reducing bacteria on the tobacco leaf to prevent additional production of TSNAs and (b) (4) during curing and the scheduled shelf life of the finished product and provided test data illustrating this inhibitory effect (see section 4.3).

The applicant provided sufficient scientific evidence and rationale that the removal of (b) (4) – a complex ingredient used in the predicate tobacco product - and addition of (b) (4) in the new tobacco product does not raise different questions of public health. Specifically, the applicant explained that the daily intake of (b) (4) from an estimated consumption rate of one can of the new tobacco product per day is within the Federal Emergency Management Agency (FEMA) possible average daily intake (PADI) for (b) (4). Additionally, the applicant provided sufficient scientific evidence and rationale that the removal of (b) (4) - a complex ingredient used in the predicate tobacco product - and addition of (b) (4) in the new tobacco product does not raise different questions of public health. (b) (4) is used as a (b) (4) agent in food and confectionery industries and is considered GRAS when used as intended in foods for human consumption (21 CFR 182.20). The applicant explained that the daily intake of (b) (4) from an estimated consumption rate of one can of the new tobacco product per day is within the FEMA PADI value for (b) (4) as used in the food industry. Although FDA has not established that GRAS status for substances used in foods is applicable for smokeless tobacco products, the GRAS designation may be informative for an adequate toxicological evaluation of the new tobacco product as compared to the predicate tobacco product. Thus, the additions of (b) (4) and (b) (4) at these levels for the new tobacco product do not cause the new tobacco product to raise different questions of public health. 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. SOCIAL SCIENCE

A social science review was completed by Amber Koblitz on September 23, 2013[5].

The final social science review did not identify any differences in characteristics between the new and predicate tobacco products that could cause the new tobacco product to raise different questions of public health from a social science perspective. 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 social science perspective.

The review also evaluated the health information summary for this SE Report. FDA has determined that the health information summary provided for this SE Report would not cause a violation of section 911 of the FD&C Act upon introduction or delivery for introduction of the new tobacco product into interstate commerce.

[5] This review evaluated the name of the new tobacco product, which at the time of the review was OS' policy; however, this information was not considered in determining the substantial equivalence of this SE Report.

5. ENVIRONMENTAL DECISION

An environmental review was completed by Catherine McCollum on October 26, 2017.

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on March 20, 2018. The FONSI was supported by an environmental assessment prepared by FDA on March 20, 2018.

6. CONCLUSION AND RECOMMENDATION

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

- Different product container closure system: plastic can with a metal lid is used in the new tobacco product instead of a plastic can with a plastic lid used in the predicate tobacco product
- A metal lid coated with (b) (4) is used in the new tobacco product instead of a plastic lid used in the predicate tobacco product
- A 1% decrease in the total amount of tobacco
- A 2% decrease in the amount of (b) (4) ((b) (4) mg/g), (b) (4) ((b) (4) mg/g), and (b) (4) tobacco ((b) (4) mg/g)
- An addition of (b) mg/g of (b) (4) tobacco and a 10% increase in the amount of (b) (4) tobacco
- A 27%, 14%, and 17% decreases in the amount of NNN (3.77 µg/g), NNK (1.16µg/g), and total TSNA (9.34 µg/g), respectively
- A 3% increase in total nicotine (b) (4) mg/g) and a 33% decrease in free base nicotine ((b) (4) mg/g)
- A decrease in the product pH in the new tobacco product (b) (4)) compared to the predicate tobacco product ((b) (4))
- A 1% increase in final tobacco moisture
- Addition of the preservative (b) (4)
- (b) (4) is used in the new tobacco product instead of (b) (4), a complex and proprietary flavor ingredient, used in the predicate tobacco product
- (b) (4) is used in the new tobacco product instead of (b) (4), a complex and proprietary flavor ingredient, used in the predicate tobacco product

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health. The applicant has sufficiently characterized the tobacco blends and ingredients added to tobacco between the new and predicate tobacco products. There were only minor differences in the tobacco blends between the new and predicate tobacco products; these differences do not cause the new tobacco product to raise different questions of public health. Additionally, the applicant provided HPHC measurements between a surrogate new tobacco product and the predicate tobacco product. The applicant provided sufficient information to demonstrate that HPHC data from the surrogate new tobacco product can be extrapolated to the new tobacco product. For this SE Report, in general, measured HPHC quantities decreased between the new and predicate tobacco products, and these differences do not cause the new tobacco product to raise different questions of public health. Additionally, there is a container closure system change in the lid material of the plastic can between the new and predicate tobacco products; a metal lid is used in the new tobacco product compared to a plastic lid

in the predicate tobacco product. Stability testing demonstrated that the change in the lid material did not affect the stability of the new tobacco product compared to the predicate tobacco product. The applicant also provided sufficient information to demonstrate that the addition of the preservative (b) (4), the use of (b) (4) instead of (b) (4), and the use of (b) (4) instead of (b) (4) in the new tobacco product compared to the predicate tobacco product do not cause the new tobacco product to raise different questions of public health. The estimated daily intake of (b) (4), (b) (4), and (b) (4) from the new tobacco product do not cause the new tobacco product to raise different questions of public health when compared to the predicate tobacco product. Additionally, (b) (4) and (b) (4) are used as GRAS ingredients whereas the predicate tobacco product used (b) (4) and (b) (4) as non-GRAS ingredients, respectively. Although FDA has not established that GRAS status for substances used in foods is applicable for smokeless tobacco products, the GRAS designation has been informative for an adequate toxicological evaluation of the new tobacco product as compared to the predicate tobacco product, and in this case, there was no difference in quantity between (b) (4) and (b) (4) and between (b) (4) and (b) (4) between the new and predicate tobacco products. 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.

The predicate tobacco product meets statutory requirements because it 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 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 products are such that the new tobacco product does not raise different questions of public health. I concur with these reviews and recommend that a 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.

A SE order letter should be issued for the new tobacco product in SE0004824, as identified on the cover page of this review.