FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0006134

SE0006134: Camel Crush	
Package Type	Box
Package Quantity	20 Cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	32%
Characterizing Flavor	Menthol
Additional Property	Crushable menthol capsule in filter
Attributes of SE Report	
Applicant	R.J. Reynolds Tobacco Company
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Combusted Filtered
Recommendation	
Issue Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

Digitally signed by Jeannie H. Jeong-im -S
Date: 2019.08.06 22:16:41 -04'00'

Jeannie Jeong-Im, 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: 2019.08.07 07:13:11 -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:

SE0006134: Camel Crush	
Product Name	Camel Light Box with Menthol Capsule
Package Type	Box
Package Quantity	20 Cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	32%
Characterizing Flavor	Menthol
Additional Property	Crushable menthol capsule in filter

The predicate tobacco product is a combusted filtered cigarette manufactured by the applicant. The applicant identified two predicate tobacco products for this SE Report: Camel Light Box with Menthol Capsule and Salem Lights Green Label prior to the start of the scientific review. On June 28, 2016, the applicant withdrew Salem Lights Green Label as a predicate tobacco product (amendment SE0013467).

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 22, 2011, FDA received an SE Report from R.J. Reynolds Tobacco Company (RJRT). On March 21, 2013, FDA received an extension request (SE0007894) from RAI Services Company (RAIS) on behalf of the applicant to allow for additional time to respond to an anticipated[1] Advice/Information Request (A/I) letter. FDA issued an Acknowledgement letter and A/I letter to the applicant on March 25, 2013. On April 1, April 5, April 9, and April 11, 2013, FDA conducted a series of teleconferences to discuss the applicant's timeline and proposal to amend the SE Report in response to the March 25, 2013 A/I letter. On April 11, 2013, FDA received an amendment (SE0008212) containing the applicant's proposed timeline for amending the SE Report. On April 17, 2013, FDA issued an Extension Response letter requesting the applicant submit a complete response to the A/I letter and any additional information prior to the start of scientific review[2] of the SE Report. On May 10, 2013, FDA issued a public health impact (PHI) A/I letter and received a response from the applicant (SE0009721) on September 6, 2013. On May 9, 2014, FDA issued a Notification letter indicating scientific review was expected to begin on June 23, 2014. FDA received an amendment (SE0010505) on May 27, 2014 clarifying the name of the predicate tobacco product in response to a request from the Office of Compliance and Enforcement (OCE) and a subsequent amendment (SE0010542) on June 20, 2014 providing a revised SE Report in

[1] At the time of the receipt of this amendment SE0007894, FDA had not issued an A/I letter for the referenced SE Report yet. In anticipation of receiving the A/I letter for this SE Report and other pending SE Reports not subject of this review, RAIS submitted this extension request of 90 days from the deadlines set forth in the A/I letter.

[2] FDA stated in this letter that, at a later date, it would issue a letter notifying RAIS of the projected scientific review start date of the SE Report.

response to the May 9, 2014 Notification letter. On October 13, 2015, FDA issued an A/I letter. On October 20, 2015, FDA received an extension request from the applicant (SE0012510) stating that RAIS intended to submit a meeting request to discuss the A/I letter. FDA issued an Extension Denied letter on October 30, 2015. On November 6, 2015, FDA received a request (AP0000014) for supervisory review of FDA's decision to deny the extension request. In response, FDA issued an Appeal Denied letter on December 11, 2015. On December 11, 2015, FDA received a response to the A/I letter (SE0012721). On June 24, 2016, FDA received an unsolicited amendment (SE0013459) correcting information in SE0012721. On June 28, 2016, FDA received the applicant's request to withdraw the second predicate tobacco product (SE0013467), Salem Lights Green Label. On September 16, 2016, FDA received an unsolicited[3] amendment (SE0013703) containing additional quantitative risk assessment (QRA) information. On April 12, 2018, FDA issued a Preliminary Finding (PFind) letter. On April 26, 2018, FDA received an extension request (SE0014649) to respond to the PFind letter. On May 7, 2018, FDA issued an Extension Granted letter. On April 10, 2019, FDA received a response to the PFind letter (SE0015191).

Product Name	SE Report	Amendments
Camel Crush	SE0006134	SE0007894 SE0008212 SE0009721 SE0010505 SE0010542 SE0012510 SE0012721 SE0013459 SE0013467 SE0013703 SE0014649 SE0015191

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 Marcella White on March 25, 2013; Ryan Nguy on October 9, 2015 and December 16, 2015; Camille Hayslett on April 17, 2019; and Sarah Vichensont on June 11, 2019.

The final review concludes that the SE Report is administratively complete.

[3] RAIS stated they submitted this amendment in anticipation of potential questions regarding their QRA methodology and conclusions within this SE Report, based upon industry meetings held with RAIS on March 2, 2016 and August 17, 2016, for SE Reports not subject of this review.

3. COMPLIANCE REVIEW

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 30, 2014, 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 Zhong Li on September 4, 2014; Kimberly Agnew-Heard on February 22, 2016[4]; and Selena Russell on May 31, 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:

- Change from non-FSC paper to FSC paper
  - 31% more (b) (4) cigarette)
  - 12% more (b) (4) /cigarette)
  - addition of (b) (4) /cigarette)
- Changes in tobacco filler ingredients
  - 32% more (b) (4) cigarette)
  - 22% more (b) (4) /cigarette)
  - 54% less (b) (4) mg/cigarette)
  - addition of (b) (4) /cigarette)
- 53% more (b) (4) in the filter (b) (4) cigarette)
- 5% less filter tow (b) (mg/cigarette)
- (b) (4) removed from tipping paper (b) (4) (b) (4) /cigarette, respectively)
- 5% more total nicotine in tobacco filler (b) (4) /cigarette)
- 11% more CO under ISO smoking regimen (1.2 mg/cigarette)
- 22% less NNK under CI smoking regimen (30.7 ng/cigarette)
- 19% less NNN under CI smoking regimen (36.9 ng/cigarette)

(b) (4) increases the solubility of menthol in cigarettes and mainstream smoke. The new and predicate tobacco products both contain a menthol capsule in the filter, which can be crushed during use to release the menthol flavoring. The 53% higher (b) (4) did not increase the smoke

[4] Addendums to the chemistry review were completed on March 7, 2016 to correct deficiencies to be conveyed to the applicant and on March 30, 2018 to clarify the discussion regarding HPHCs that were deferred to toxicology for further evaluation.

yields of menthol of the cigarette with the crushed capsule, which were 1% (ISO) and 9% (CI) lower in the new tobacco product than in the predicate tobacco product.[5] Deletion of (b) (4) (b) (4) color and extender from the tipping paper are not expected to impact smoke HPHCs since the ingredients are being removed and the tipping paper is not combusted, and therefore, this deletion does not cause the new tobacco product to raise different questions of public health. Increases in (b) (4) as well as the addition of (b) (4) (b) (4) and decrease of (b) (4) are less than cigarette but may affect HPHC values. Also, the filter tow decreased by 5% and the tobacco cut size decreased by 11% (deferred from engineering), which may increase TNCO. The cigarette paper changed from non-FSC to FSC paper, which resulted in an increase in (b) (4) due to the introduction of FSC bands. These changes may increase smoke TNCO and HPHCs. The applicant provided tobacco filler HPHC data for ammonia, arsenic, cadmium, total nicotine, NNK, and NNN, and provided mainstream smoke data for tar, nicotine, carbon monoxide, NNK, NNN, ammonia, benzo(a)pyrene, acetaldehyde, acrolein, crotonaldehyde, formaldehyde, 1,3-butadiene, acrylonitrile, benzene, isoprene, toluene, 1-aminonaphthalene, 2-aminonaphthalene, and 4-aminobiphenyl under the ISO and CI regimens.[6] The data for the new and predicate tobacco products were compared by Two One-Sided T-test (TOST).[7] An increase in nicotine was noted in tobacco filler (5% increase, 0.6 mg/cigarette) between the new and predicate tobacco product, which is not analytically equivalent. However, nicotine in smoke yields under both ISO and CI) was analytically equivalent between the new and predicate tobacco products. Therefore, the increase in nicotine in tobacco filler does not cause the new tobacco product to raise different questions of public health. On the other hand, higher smoke yields in carbon monoxide (11% increase under ISO) and lower smoke yields in NNK (22% decrease under CI) and NNN (19% decrease under CI) in the new tobacco product were not analytically equivalent compared to the predicate tobacco product. The CO, NNN, and NNK differences were deferred to toxicology for further evaluation. 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 Ryan Foringer on August 29, 2014; Julie Morabito on February 16, 2016[8]; and Ryan Andress on May 30, 2019.

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:

[5] The applicant also provided ISO and CI menthol data on the cigarette with the uncrushed, intact capsule. The cigarette with the intact capsule released less menthol than the limit of quantitation for mainstream smoke (ISO and CI regimens).
[6] Except for menthol data, as described previously, the applicant provided HPHC data in tobacco filler and mainstream smoke on cigarettes with a crushed capsule, which is expected to have higher HPHC yields than the cigarette with an intact capsule.
[7] (a) Division of Product Science, Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration. *Internal Memorandum: Equivalent Testing for SE Evaluations (February 24, 2017)*; Silver Spring, Maryland, USA, 2017, and (b) Division of Product Science, Office of Science, Center for Tobacco Products, U.S. Food and Drug Administration. *Addendum to February 24, 2017, Equivalence Testing for SE Evaluations Memo (April 15, 2019)*; Beltsville, Maryland, USA, 2019.
[8] An addendum to the Engineering review was completed on April 6, 2016 to correct typographical errors in a deficiency.

- Change from non-FSC paper to FSC paper
- Tobacco cut size (CPI): 11% decrease
- Tobacco filler mass: 1% increase
- Tobacco rod density: 1% increase
- Cigarette paper base paper porosity: 58% increase
- Filter density: 2% increase
- Filter pressure drop: 3% decrease

The tobacco cut size of the new tobacco product decreased by 11% compared to the predicate tobacco product. A decrease in tobacco cut size may cause changes in smoke chemistry and is deferred to chemistry for an evaluation of TNCO. The new tobacco product has a 58% increase in cigarette paper base paper porosity, which may raise TNCO. An evaluation of the TNCO data in the 1st engineering review showed increases of less than 5.3% between the new and predicate tobacco products.[9] Therefore, the increase in cigarette paper base paper porosity does not cause the new tobacco product to raise different questions of public health. The new tobacco product has less than 3% differences in tobacco filler mass, tobacco rod density, filter density, and filter pressure drop compared to the predicate tobacco product. These minor differences in the new tobacco product are not expected to substantially increase tar, nicotine, and other HPHC yields compared to the predicate tobacco products. The new tobacco product uses FSC paper, and the predicate tobacco product uses non-FSC paper, which may raise TNCO in the new tobacco product. The engineer referenced toxicology's memorandum on toxicological implications of FSC paper[10] and stated that the addition of bands due to a change from non-FSC to FSC paper does not cause the new tobacco product to raise different questions of public health. However, according to OS' current review process, engineering should have deferred the evaluation of HPHCs that may be impacted by FSC paper change to chemistry and toxicology as there were other changes such as ingredient and design changes (*see* chemistry and toxicology sections for discussion of HPHCs). 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. TOXICOLOGY

Toxicology reviews were completed by Mamata De on October 2, 2015 and Pei-Hsuan Hung on April 3, 2018 and June 7, 2019.

The final 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

[9] The August 29, 2014, engineering review identified differences in cigarette paper base paper porosity and evaluated the applicant's TNCO data, which at the time of the review was OS' policy. The August 29, 2014, engineering review determined that the reported increases of 0.8% in tar, 5.3% in nicotine, and 3.7% in carbon monoxide in the new tobacco product compared to the predicate tobacco product did not cause the differences in cigarette paper base paper porosity to raise different questions of public health.

[10] See July 17, 2017, memo entitled, "Toxicological Implications of FSC Paper."

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

- Increase in CO by 11% or 1.2 mg/cigarette (ISO)
- Decrease in NNK by 22% (CI)
- Decrease in NNN by 19% (CI)

The HPHC data analysis by chemistry identified analytically non-equivalent increase in CO under the ISO smoking regimen and analytically non-equivalent decreases in NNK and NNN under the CI smoking regimen. From a toxicological perspective, decreases in NNK and NNN are not of concern because it reduces cancer risks to the user. The increased CO in the new tobacco product is 1.2 mg/cigarette or an 11% increase in CO compared to the predicate tobacco product. However, the CO concentration (ppm) in smoke from the new tobacco product is not higher than the CO smoke concentration from the predicate tobacco product on a per puff basis. From the toxicological perspective, this change is not expected to increase CO exposure to smokers of 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 toxicology perspective.

4.4. SOCIAL SCIENCE

Social science reviews were completed by Amber Koblitz on September 26, 2014, and Jennifer Bernat on January 28, 2016.

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.[11] 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 social science perspective.

4.5. BEHAVIORAL AND CLINICAL PHARMACOLOGY

A behavioral and clinical pharmacology review was completed by Allison Hoffman on August 11, 2014.[12]

The behavioral and clinical pharmacology review did not identify any differences in characteristics between the new and predicate tobacco products that could cause the new tobacco products to raise different questions of public health from a behavioral and clinical pharmacology perspective. Therefore, the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise

[11] The final social science review dated January 28, 2016 identified a deficiency for the new tobacco product compared to Salem Lights Green Label. An addendum review was completed on April 11, 2018 to indicate that the deficiency is now moot as a result of the applicant withdrawing Salem Lights Green Label as a predicate tobacco product on June 28, 2016. Therefore, no social science deficiencies remain.

[12] The behavioral and clinical pharmacology review stated that ventilation increased by 28% in the new product compared to the 2nd predicate product, Salem Lights Green Label Box. However, that predicate produce was withdrawn on June 28, 2016.

different questions of public health related to consumer use of the product and impact on exposure and behavior.

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 (SE0006134) 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:

- Change from non-FSC paper to FSC paper
  - 31% more (b) (4) /cigarette)
  - 12% more (b) (4) /cigarette)
  - addition of (b) (4) /cigarette)
- Changes in tobacco filler ingredients
  - 32% more (b) (4) /cigarette)
  - 22% more (b) (4) /cigarette)
  - 54% less (b) (4) /cigarette)
  - addition of (b) (4) /cigarette)
- 53% more (b) (4) in the filter (b) (4) cigarette)
- (b) (4) color and extender removed from tipping paper (b) (4) cigarette, respectively)
- 5% less filter tow (7 mg/cigarette)
- 5% more total nicotine in tobacco filler (0.6/mg/cigarette)
- 11% decrease in tobacco cut size
- 58% increase in cigarette paper base paper porosity
- Increase in CO by 11% (ISO) (1.2 mg/cigarette)
- Decrease in NNK by 22% (CI) (30.7 ng/cigarette)
- Decrease in NNN by 19% (CI) (36.9 ng/cigarette)

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health. A difference between the new and predicate tobacco products is a change from non-FSC to FSC cigarette paper. This change is the basis for the change in cigarette paper ingredients and the increase in cigarette paper base porosity which may impact HPHCs including TNCO. Compared to the predicate tobacco product, the new tobacco product has ingredient increases (increase in (b) (4), (b) (4), and (b) (4) quantities), and differences in design parameters (e.g., increase in cigarette paper base porosity and decreases in filter tow and tobacco cut size). Although there was an increase in nicotine in tobacco filler (5% increase, 0.6 mg/cigarette) between the new and predicate tobacco product, the nicotine in smoke yields (under both ISO and CI) was analytically equivalent between the new and predicate tobacco products. Deletion of (b) (4) color and

extender from the tipping paper are not expected to impact smoke HPHCs since the ingredients are being removed and the tipping paper is not combusted. The applicant provided mainstream smoke data for tar, nicotine, carbon monoxide, NNK, NNN, ammonia, benzo(a)pyrene, acetaldehyde, acrolein, crotonaldehyde, formaldehyde, 1,3-butadiene, acrylonitrile, benzene, isoprene, toluene, 1-aminonaphthalene, 2-aminonaphthalene, and 4-aminobiphenyl under the ISO and CI smoking regimens. There were only three HPHCs that were determined to be not analytically equivalent in the new tobacco product: 11% higher CO, 22% lower NNK, and 19% lower NNN. Decreases in NNK and NNN reduce cancer risks to the user. The increased CO in the new tobacco product is 1,2 mg/cigarette or 11%. However, the CO concentration (ppm) in smoke from the new product is not higher than the CO smoke concentration from the predicate product on a per puff basis. From the toxicological perspective, this change is not expected to increase CO exposure to smokers of the new tobacco product. 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 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).

Because the proposed action is issuing an SE order for this 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 SE0006134, as identified on the cover page of this review.