U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0014246

SE0014246: Eclipse	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Ventilation	24%
Characterizing Flavor	None
Source of Energy	Carbon heat source
Common Attributes of SE Reports	
Applicant	R.J. Reynolds Tobacco Company
Report Type	Regular
Product Category	Cigarette
Product Sub-Category	Non-Combusted
Recommendation	
Issue a Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

Todd L. Cecil -S
Digitally signed by Todd L. Cecil -S
Date: 2018.07.19 09:04:32 -04'00'

Todd Cecil, Ph.D.
Associate 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: 2018.07.19 10:04:53 -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 product:

SE0014246: Eclipse	
Product Name	Eclipse Menthol
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Ventilation	24%
Characterizing Flavor	Menthol
Source of Energy	Carbon heat source

The predicate tobacco product is a non-combusted cigarette manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On August 17, 2017, RAI Services Company (RAIS), submitted a regular SE Report (SE0014246) on behalf of R.J. Reynolds Tobacco Company (RJRT). On August 23, 2017, FDA issued an acknowledgment letter. On October 26, 2017, FDA issued an Advice/Information Request (A/I) letter for SE0014246. On December 21, 2017, FDA received RJRT's response to the A/I letter (SE0014446). On March 21, 2018, FDA issued an A/I letter to request information for the Environmental Assessment (EA).[1] On April 20, 2018, FDA received RJRT's response to the A/I letter (SE0014638). On June 28, 2018, FDA requested additional information for the EA. On July 5, 2018, FDA received the applicant's response (SE0014806). The new tobacco product name and the submission tracking numbers for the SE Report and Amendments are tabulated below:

Product Name	SE Report	Amendments
Eclipse	SE0014246	SE0014446 SE0014638 SE0014806

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 Nia White on August 23, 2017.

This review concludes that the SE Report is administratively complete.

[1] *See* April 19, 2018, memo to file.

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 September 1, 2017, concluded that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco product is grandfathered and, therefore, an eligible predicate tobacco product.

OCE also completed reviews to determine whether the new tobacco product is in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act) (see section 910(a)(2)(A)(i)(II) of the FD&C Act). The OCE reviews dated February 22, 2018 and July 10, 2018 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 Lida Oum on October 16, 2017 and February 12, 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 that the differences do not cause the new tobacco product to raise different questions of public health. The review identified the following differences:

- Higher amounts of (b)(4) tobacco (16%), (b) (4) in the adhesives in the heated portions of the tobacco product (23%), (b) (4) (100%), and (b) (4) (303%) in the new tobacco product as compared to the predicate tobacco product
- Addition of (b) (4) mg/cig) to the new tobacco product
- Lower nicotine yields (CI 61%, ISO 76%) in the new tobacco product
- Increased formaldehyde yield (ISO 96%) in the new tobacco product
- Removal of menthol in the new tobacco product

The differences in (b) (4), nicotine, and menthol in the new tobacco product compared to the predicate tobacco product were deferred, respectively, to Toxicology, Behavioral and Clinical Pharmacology (BCP), and Social Science, for further evaluation. The applicant provided harmful and potentially harmful constituent (HPHC) measurements for B[a]P, acetaldehyde, formaldehyde, and acrolein to address the differences in (b) (4) in the new tobacco product compared to the predicate tobacco

product. The submitted HPHC methods are suitable[2] and the HPHC data is valid[3]; therefore, HPHC data are acceptable from a chemistry perspective and may be further evaluated for clinical and non-clinical relevance. The reported B[a]P, acetaldehyde, acrolein, and other HPHC values (except for formaldehyde) are lower in the new tobacco product or not statistically different than the predicate tobacco product and therefore do not cause the new tobacco product to raise different questions of public health. Formaldehyde is reported to be higher by 96% under the ISO regimen in the new tobacco product compared to the predicate tobacco product. The statistical evaluation indicates that the difference in formaldehyde between the new and predicate tobacco products is statistically significant. Thus, the increase of formaldehyde under ISO regimen is 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 related to product chemistry.

4.2. ENGINEERING

Engineering reviews were completed by Karen Coyne on October 16, 2017 and February 02, 2018.

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:

- 32% increase in cigarette draw resistance
- 20% decrease in TBR[4] tobacco filler mass
- 5% decrease in SUB[5] tobacco filler mass
- 54% increase in SUB tobacco rod density
- 15% increase in HSA[6] cigarette paper base paper porosity
- Addition of a filter
- 110% increase in filter/tube length
- 0.8% increase in cigarette mass
- 32% decrease in pack moisture
- 10% decrease in TBR[4] tobacco moisture
- 8% decrease in SUB[5] tobacco moisture
- 14% decrease in TBR[4] tobacco rod density
- 14% increase in filter tipping paper length

[2] The applicant has demonstrated that the analytical methods and procedures are capable of measuring each analyte with precision, accuracy, and sensitivity that are appropriate for the comparison of the HPHC content of the new and predicate tobacco products at the concentrations reported.
[3] The data presented in the SE Reports were collected using an analytical method that has been validated in a manner similar to appropriate international standards (such as ICH Q2R) and with sufficient replicates to allow comparisons between the new and predicate tobacco products.
[4] Tobacco Roll Rod.
[5] Substrate.
[6] Heat Source Assembly.

- Decrease in the lengths of the FEP[7], OFP[8], SUB[5], and TBR[4] segments
- Removal of HSA[6] tobacco filler
- Increase in filter segment weight (due to the addition of a functional filter)
- Increase in FEP[7] overwrap basis weight
- Decrease in OFP[8] tipping paper basis weight
- Decrease in the OFP[8] rod weight partly due to the decrease in segment length
- Decrease in OFP[8] rod pressure drop
- Change in OFP[8] wrap

The design parameter changes to the cigarette draw resistance, TBR[4] tobacco filler mass, SUB[5] tobacco filler mass, tobacco rod density, cigarette paper base paper porosity, and addition of a filter each tend to decrease the smoke constituent yields and thus does not cause the new tobacco product to raise different questions of public health. The increase in cigarette mass between the new and predicate tobacco products is small, and therefore is not expected to result in any changes in smoke constituent yields and thus does not cause the new tobacco product to raise different questions of public health. The design parameter changes to the pack moisture, tobacco moisture, TBR,[4] and filter tipping paper length may increase smoke constituent yields. The potential increase in HPHC yields is deferred to the chemistry and toxicology reviews.

The changes in the segment lengths and the OFP[8] rod weight occurred due to incorporation of a functional filter in the new tobacco product. The addition of such a filter is expected to reduce the HPHC contents in the smoke yields. The decrease in tobacco filler is similarly expected to reduce smoke constituent yields. These changes to structural wraps and papers do not impact smoke HPHC yields. The decrease in OFP[8] rod pressure drop is more than offset by the filter pressure drop, resulting in an increase in overall cigarette draw resistance.

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 related to product engineering.

4.3. TOXICOLOGY

Toxicology reviews were completed by Ana DePina on October 20, 2017 and February 12, 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 difference does not cause the new tobacco product to raise different questions of public health. The review identified the following difference:

- Increased formaldehyde yield (ISO 96%)

To address whether differences in tobacco blends, and increases in single and complex ingredients in the new tobacco product (including (b) (4) may impact HPHCs and cause the

[7] Front End Piece.
[8] Outer Front Piece.

new tobacco product to raise different questions of public health, the applicant provided HPHC yields under ISO and CI smoking regimens. ISO yield of formaldehyde is increased, however, based on the totality[9] of HPHC data, and quantitative Risk analysis provided by the applicant, the increase in formaldehyde yield measured by ISO does not cause the new tobacco product to raise different questions of public health.

Therefore, the differences in characteristics between the new and corresponding predicate tobacco product do not cause the new tobacco product to raise different questions of public health related to toxicology.

4.4. SOCIAL SCIENCE

A social science review was completed by Jennifer Bernat on October 6, 2017.

The final social science review concludes that the new tobacco product has different characteristics from the predicate tobacco product, but the difference does not cause the new tobacco product to raise different questions of public health from a social science perspective. The review identified the following difference:

- Removal of characterizing flavor (menthol)

The appeal of menthol cigarettes, especially among youth, has been linked to their portrayal in marketing as having a smoother taste and being less harsh, which may be appealing to newer smokers or those curious about experimentation. Therefore, the addition of a characterizing flavor or a change in a characterizing flavor may increase initiation behavior or change usage behavior or otherwise cause a product to raise different questions of public health. However, studies do not suggest that the absence of menthol (i.e., lack of menthol as a characterizing flavor) would increase the appeal to new smokers. The differences in flavor between the new and predicate tobacco products are changes from a characterizing flavor to a non-characterizing flavor. Therefore, the difference in characteristics between the new and predicate tobacco products does not cause the new tobacco product to raise different questions of public health from a social science perspective.

4.5. BEHAVIORAL AND CLINICAL PHARMACOLOGY (BCP)

A BCP review was completed by Theresa Carbonaro on February 13, 2018.

The final BCP 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 difference does not cause the new tobacco product to raise

[9] Analytes and relative decreases reported by the applicant include: acetaldehyde (↓67%), acrolein (↓72%), acetone (↓75%), crotonaldehyde (↓75%), propionaldehyde (↓68%), methyl ethyl ketone (↓67%). The analytes that are reported to be below the limit of detection include: B[a]P, 1,3-butadiene, ethylene oxide, vinyl chloride, propylene oxide, acrylonitrile, isoprene, benzene, toluene, phenol, catechol, o-cresol, and m,p-cresol.

different questions of public health from a BCP perspective. The review identified the following difference:

- Decreased nicotine yields (CI 61%, ISO 76%)

Nicotine is the primary addictive substance in tobacco products. Changes in the amount and rate of nicotine delivery to the user can significantly impact addictiveness and dependence of the product. The applicant's statement, that both products are above the "addictive threshold," does not factor into FDA's review, which is focused on whether there are differences in characteristics between the predicate and new tobacco products which cause the new tobacco product to raise different questions of public health. The applicant provided nicotine content data under ISO and CI smoke regimens; nicotine yields were lower in the new tobacco product compared to the predicate tobacco product. Nicotine is an addictive substance, so the reduction in nicotine content and smoke yields in the new tobacco product does 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 BCP perspective.

5. ENVIRONMENTAL DECISION

An environmental review was conducted by Mehran Niazi on March 20, 2018.

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on July 17, 2018. The FONSI was supported by an environmental assessment prepared by FDA on July 17, 2018.

6. CONCLUSION AND RECOMMENDATION

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

- Increased (b)(4) tobacco
- Addition of (b)(4) tobacco
- Increased (b) (4)
- Increased (b) (4)
- Increased (b) (4)
- Removal of menthol
- Lower nicotine smoke yields (ISO and CI)
- Increased formaldehyde yield (ISO only)
- Increase in cigarette draw resistance
- Decrease in TBR tobacco filler mass
- Decrease in SUB tobacco filler mass
- Increase in SUB tobacco rod density
- Increase in HSA cigarette paper base paper porosity
- Addition of a filter Increase in cigarette mass

- Decrease in pack moisture
- Decrease in TBR tobacco moisture
- Decrease in SUB tobacco moisture
- Decrease in TBR tobacco rod density
- Increase in filter tipping paper length
- Decrease in the lengths of FEP, OFP, SUB, and TBR segments
- Decrease in OFP rod pressure drop
- Change in OFP wrap
- Removal of HSA tobacco filler
- Increase in filter segment weight (due to the addition of a functional filter)
- Increase in FEP overwrap basis weight
- Decrease in OFP tipping paper basis weight
- Decrease in the OFP rod weight

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 are constructed with four distinct regions that contain tobacco and one components that does not contain tobacco. The four regions that contain tobacco are the heat source, the substrate, the overwrap and the tobacco roll rod. The component that does not contain tobacco is the filter.

Heat Source

The heat source contains a small quantity of tobacco and a carbon disk. In the new and predicate tobacco products, the tobacco in the heat source is combusted to heat a non-combustible carbon disk heat source. The combusted portion of the new tobacco product contains less tobacco (all (b)(4) tobacco), than the predicate tobacco product. The reduction in the amount of combusted tobacco will reduce HPHC content and does not cause the new tobacco product to raise different questions of public health.

Substrate and Tobacco Rod Roll

The substrate abuts the heat source and contains (b) (4) . The tobacco rod roll contains tobacco (b)(4) . The applicant states that both the substrate and the tobacco rod roll in the new tobacco product contain higher amounts of (b)(4) l tobacco than the predicate tobacco product. The increase in (b)(4) tobaccos may result in increases in B[a]P in combusted cigarettes. However, the applicant provided data that indicates an absence (ISO) or decrease (CI) in B[a]P in the new tobacco product. Therefore, the changes in tobacco in the (b) (4) do not cause the new tobacco product to raise different questions of public health. Changes in (b) (4) additives to the tobacco rod roll may lead to an increase in HPHCs. The applicant provided data that demonstrates a decrease in all HPHCs except for formaldehyde under the ISO regimen[10]. All HPHCs that the applicant measured, except formaldehyde, showed

[10] Analytes reported to decrease by the applicant include: acetaldehyde, acrolein, acetone, crotonaldehyde, propionaldehyde, methyl ethyl ketone. The analytes that are reported to be below the limit of detection include: B[a]P, 1,3-butadiene, ethylene oxide, vinyl chloride, propylene oxide, acrylonitrile, isoprene, benzene, toluene, phenol, catechol, o-cresol, and m,p-cresol for the new and predicate tobacco products.

decreases or were absent under the CI regimen. However, based on the totality of the data presented[11] by the applicant, the increase in formaldehyde in smoke yields does not cause the new tobacco product to raise different questions of public health. The design parameter changes to the tobacco rod roll tobacco filler mass, substrate tobacco filler mass, tobacco rod density, cigarette paper base paper porosity each tend to decrease HPHC yields. This is reflected (except for formaldehyde) in the measured HPHC values provided by the applicant. The formaldehyde increase was found to be small enough relative to the decreases in other HPHCs to not cause the new tobacco product to raise different questions of public health. Thus, the changes to tobacco filler masses, tobacco rod density, cigarette paper base paper porosity do not cause the new tobacco product to raise different questions of public health. The applicant provided nicotine content data under ISO and CI smoke regimens; nicotine yields were lower in the new tobacco product compared to the predicate tobacco product. Nicotine is an addictive substance, so the reduction in nicotine content and smoke yields in the new tobacco product does not cause the new tobacco product to raise different questions of public health.

Overwrap

The overwrap consists of cigarette paper, tipping paper, product structural elements, and adhesives. The overwrap is heated, but not combusted. (b) (4) may break down through pyrolysis to form HPHCs, however, the overwrap constituents are not combusted. Because (b) (4) will not enter the mainstream or sidestream smoke, changes to (b) (4) in the adhesives does not cause the new tobacco product to raise different questions of public health. The increase in cigarette mass (0.8%) between the new and predicate tobacco product is small, and therefore does not cause the new tobacco product to raise different questions of public health. The design parameter changes to the pack moisture, tobacco moisture, and filter tipping paper length may increase TNCO yields. The measured TNCO values of the new tobacco product were lower (10-84%) than the values for the predicate tobacco product. Thus, the changes to pack moisture, tobacco moisture, and filter tipping paper length do not cause the new tobacco product to raise difference questions of public health. The changes in the segment lengths and the OFP rod weight occurred due to incorporation of a functional filter in the new tobacco product and the addition of a filter is expected to reduce the HPHC smoke yields. Additionally, the decrease in tobacco filler mass is expected to reduce smoke constituent yields. The changes to structural wraps and papers filter segment weight, FEP overwrap, OFP tipping paper, OFP rod weight do not impact smoke HPHC yields. The decrease in OFP rod pressure drop is offset by the filter pressure drop, resulting in an increase in overall cigarette draw resistance.

Filter

Changes to (b) (4) in a filter may reduce some of the volatile and semi-volatile compounds of smoke constituents. Thus, the increase of (b) (4) in the filter of the new tobacco product compared to the predicate does not cause the new tobacco product to raise different questions of public health. The design parameter changes to the cigarette draw resistance, filter total denier, denier per filament, filter density, filter length, and filter pressure drop each tend to decrease HPHC yields. This is reflected (except for formaldehyde) in the measured HPHC values provided by the applicant. The formaldehyde increase was found to be small enough relative to

[11] The totality of the data presented is a consideration of the reduction in all of the reported HPHCs relative to the HPHCs that are reported to increase. In this case, the increase in formaldehyde was small from an absolute exposure perspective and the decreases in HPHC yields for other HPHCs were larger from an absolute exposure perspective. Thus the toxicology reviewer found the overall toxin exposure to be a net decrease (note: the toxin exposure also accounts for the relative toxicity of the all HPHCs in the analysis).

the decreases in other HPHCs to not cause the new tobacco product to raise different questions of public health. Thus, the changes to cigarette draw resistance, filter total denier, denier per filament, filter density, filter length, and filter pressure drop 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.

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 product do not cause the new tobacco product to raise different questions of public health. I concur with these reviews and recommend that an SE order letter be issued.

FDA examined the environmental effects of finding the new tobacco product substantially equivalent and made a finding of no significant impact.

An SE order letter should be issued for the new tobacco product in SE0014246, as identified on the cover page of this review.