FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0014221

SE0014221: 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
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):

Digitally signed by Colleen K. Rogers -S
Date: 2018.07.19 09:37:57 -04'00'

Colleen K. Rogers, Ph.D.
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 10:07:30 -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:

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

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On July 31, 2017, FDA received an SE Report from RAI Services Company (RAIS) on behalf of R.J. Reynolds Tobacco Company (RJRT). On August 7, 2017, FDA received an amendment with a correction to the cover letter of the SE Report (SE0014232). Also on August 7, 2017, FDA issued an Acknowledgment letter. FDA issued an Advice/Information Request (A/I) letter on October 27, 2017. On December 21, 2017, FDA received the applicant's response to the A/I letter (SE0014448). FDA issued a Preliminary Finding (PFind) letter on March 21, 2018. On April 4, 2018, the applicant contacted FDA to request clarification on the March 21, 2018, PFind letter. Given the unique circumstances that only environmental requests remained, the PFind letter was reissued on April 20, 2018, as an A/I letter to request information for the Environmental Assessment, but with a 30-day response timeframe.[1] On May 11, 2018, FDA received the applicant's response to the A/I letter (SE0014716). On June 28, 2018, FDA requested additional information for the Environmental Assessment. On July 5, 2018, FDA received the applicant's response (SE0014806).

Product Name	SE Report	Amendments
Eclipse Menthol	SE0014221	SE0014232 SE0014448 SE0014716 SE0014806

1.3. SCOPE OF REVIEW

This review captures all regulatory, compliance, and scientific reviews completed for this SE Report.

[1] *See* April 19, 2018, and July 18, 2018, memos to file.

2. REGULATORY REVIEW

A regulatory review was completed by Lea Lakes on August 7, 2017.

The review concludes that the SE Report is administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed a review to determine whether the applicant established that the predicate tobacco product is a grandfathered product (i.e., was commercially marketed in the United States other than exclusively in test markets as of February 15, 2007). The OCE review dated September 1, 2017, concludes that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco product is grandfathered and, therefore, is an eligible predicate tobacco product.

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) (see section 910(a)(2)(A)(i)(II) of the FD&C Act). The OCE reviews dated June 21, 2018, and July 10, 2018, conclude that the new tobacco product is in compliance with the FD&C Act.

4. SCIENTIFIC REVIEW

The new and predicate tobacco products have a non-combusted cigarette design, consisting of the following major sub-assemblies: heat source assembly (HSA), tobacco substrate (SUB), tobacco roll rod (TBR), and filter tip. The HSA consists of a carbon heat source, which is a (b)(4) [redacted]

Scientific reviews were completed by the Office of Science (OS) for the following disciplines:

4.1. CHEMISTRY

Chemistry reviews were completed by Melissa McCulloch on October 10, 2017, and An Vu on February 8, 2018.

The 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:

- 15% decrease in total amount of tobacco
- Removal of tobacco from the heat source assembly (HSA) heat source

- Change from [redacted] to [redacted] into [redacted] in the tobacco substrate (SUB) section
- Change in tobacco blend in the tobacco roll rod (TBR), including the removal of [redacted] mg/cigarette)
- 13% increase in menthol
- Addition of two complex flavor ingredients ([redacted]) and removal of three complex flavor ingredients ([redacted])

The applicant provided quantities of tobacco in all components of the new and predicate tobacco products that contain tobacco, including the HSA heat source, HSA tobacco paper, tobacco substrate (SUB), and tobacco roll rod (TBR) sections. The removal of tobacco from the HSA heat source and the overall decrease in total amount of tobacco in the new tobacco product would not lead to an increase in harmful or potentially harmful constituents (HPHCs) and, thus, does not cause the new tobacco product to raise different questions of public health. In addition, the tar, nicotine, and carbon monoxide (TNCO) data submitted by the applicant confirm that there was no increase in nicotine or CO. In the SUB section, [redacted] produced from [redacted] in the predicate tobacco product are replaced by [redacted] in the new tobacco product. Higher amounts of [redacted] could impact smoke yields of HPHCs, particularly benzo[a]pyrene (B[a]P). The applicant provided HPHC data, including B[a]P smoke yields, for the new and predicate tobacco products under both ISO and Canadian Intense (CI) machine smoking regimens. Yields of B[a]P are comparable between the new and predicate tobacco products under both ISO and CI regimens. Therefore, the increase in [redacted] does not cause the new tobacco product to raise different questions of public health. In the TBR section, [redacted] produced from [redacted] in the predicate tobacco product are replaced by lower amounts of [redacted] in the new tobacco product, which would not lead to an increase in HPHCs and thus does not cause the new tobacco product to raise different questions of public health. However, there are moderate amounts of [redacted] present in the new tobacco product that are absent in the predicate tobacco product. An increase in these tobacco types may lead to an increase in certain HPHCs, such as B[a]P. As stated above, yields of B[a]P are comparable between the new and predicate tobacco products. In addition, the levels of several other HPHCs[2] were lower in the new tobacco product under both ISO and CI smoking regimens, except for one (formaldehyde under ISO conditions). As explained in the toxicology review (see section 4.3), these differences in HPHC levels do not cause the new tobacco product to raise different questions of public health.

The HPHC data provided by the applicant demonstrate that differences in complex flavor ingredients do not cause the new tobacco product to raise different questions of public health. The new tobacco product had 48% lower menthol smoke yields compared to the predicate tobacco product under the ISO smoking regimen. However, the new tobacco product had 10%

[2] Analytes and relative decreases under the ISO smoking regimen reported by the applicant include: acetaldehyde (↓67%), acrolein (↓71%), acetone (↓75%), crotonaldehyde (↓75%), propionaldehyde (↓69%), and methyl ethyl ketone (↓67%). The analytes that are reported to be below the limit of quantitation 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.

higher menthol smoke yields under the CI smoking regimen, which is larger than experimental variability. Higher amounts of menthol in the new tobacco product could potentially affect the appeal of the new tobacco product and was deferred to social science for review. Although there is a 13% increase in the amount of menthol added to the new tobacco product ((b) (4) mg/cig vs. (b) (4) mg/cig), I note that the menthol levels in both products exceed the reported threshold limit (approximately 0.6 mg/cig) needed to impart sensory effects and fall within the lower range of menthol levels measured in a survey of commercial mentholated cigarettes (2.9 to 19.6 mg/cig).[3,4] Furthermore, although the new tobacco product has a different target value and wider range specification than the predicate tobacco product for added menthol, the upper range of menthol added to the predicate tobacco product encompasses the new tobacco product target value and the lower range of menthol added to the new tobacco product encompasses the predicate tobacco product target value. The menthol range for the new tobacco product, while wider than that of the predicate tobacco product, is not overly broad. Therefore, the difference in menthol levels between the new and predicate tobacco products 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 chemistry perspective.

4.2. ENGINEERING

Engineering reviews were completed by James Cheng on October 17, 2017, and February 5, 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:

- Removal of tobacco from the heat source assembly (HSA) heat source ((b) (4))
- Change in OFP tipping paper from paper/foil/paper laminate to paper
- Change in FEP overwrap from paper to paper/foil/paper laminate
- 32% increase in cigarette draw resistance
- 32% decrease in pack moisture
- 5% decrease in SUB tobacco filler mass
- 20% decrease in TBR tobacco filler mass
- 54% increase in SUB tobacco rod density
- 14% decrease in TBR tobacco rod density
- 38% decrease in SUB length

[3] Ai, J.; Taylor, K.M.; Lisko, J.G.; Tran, H.; Watson, C.H.; and Holman, M.R. Menthol Content in US Marketed Cigarettes. *Nicotine Tob Res*. 2016;18(7):1575-80.

[4] Menthol levels were measured in whole combustible cigarettes; however, the methods used to obtain these data did not include combustion of the samples. Based on the product design characteristics of Eclipse Menthol, this conclusion does not differ from that of the combustible cigarettes utilized for this method.

- 8% decrease in TBR length
- 15% increase in HSA cigarette paper base paper porosity
- Incorporation of a functional filter, which includes the following changes to the filter design:
    - 110% increase in total filter length
    - 22% decrease in total denier (hollow segment)
    - 52% increase in denier per filament (hollow segment)
    - 14% decrease in filter density
    - Increase in pressure drop
    - 14% increase in tipping paper length

The removal of tobacco from the heat source assembly (HSA) heat source does not cause the new tobacco product to raise different questions of public health since TNCO testing confirms that the new tobacco product has reduced TNCO yields compared to the predicate tobacco product. The design parameter changes to the cigarette draw resistance, SUB tobacco filler mass, TBR tobacco filler mass, SUB tobacco rod density, TBR tobacco rod density, cigarette paper base paper porosity, filter total denier, denier per filament, filter density, total filter length, and filter pressure drop each tend to decrease smoke constituent yields and, thus, do not cause the new tobacco product to raise different questions of public health. TNCO testing confirms that the new tobacco product has reduced TNCO yields compared to the predicate tobacco product. Since the new tobacco product is not combusted, moisture does not affect aerosol yields the way it would affect a combusted cigarette. For a non-combusted cigarette, aerosol production is generally affected by glycerin levels. As such, the decrease in pack moisture does not cause the new tobacco product to raise different questions of public health. This determination is further supported by the HPHC data the applicant submitted (described in section 4.3).

The changes in the SUB, TBR, and filter segment lengths occurred due to incorporation of a functional filter in the new tobacco product. The filter mouthpiece is a hollow cellulose acetate (CA) tube in the predicate tobacco product, which functions as a mouthpiece and spacer and does not function as a filter. In the new tobacco product, the hollow CA filter is combined with a functional CA filter using filter plug wrap. The filter segment of the new tobacco product has a pressure drop and provides aerosol filtration. The addition of such a filter is expected to reduce tobacco smoke constituent yields and TNCO testing confirms that the new tobacco product has reduced TNCO yields compared to the predicate tobacco product. The changes to structural wraps and papers (OFP tipping paper and FEP overwrap) do not impact smoke HPHC yields. 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 Ana Depina on October 5, 2017, and February 15, 2018.

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

identified the following differences:

- Differences in tobacco blend
- Differences in tobacco additive ingredients, including complex ingredients (i.e., (b) (4) [redacted])
- 119% increase in formaldehyde smoke yield (ISO smoking regimen only)

To address whether differences in tobacco blends and increases in single and complex ingredients in the new tobacco product may impact HPHCs, the applicant provided smoke yields of 20 HPHCs under both ISO and CI smoking regimens. The ISO yield of formaldehyde is increased; however, based on the totality[5] of HPHC data and quantitative risk assessment provided by the applicant, the increase in formaldehyde ISO yield (from (b) (4) micrograms/ cigarette in the predicate tobacco product to (b) (4) micrograms/cigarette in the new tobacco product) does not cause the new tobacco product to raise different questions of public health from a toxicology 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 toxicology perspective.

4.4. SOCIAL SCIENCE

A social science review was completed by Katherine Margolis on October 2, 2017.

The 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. The new and predicate tobacco products both have a characterizing flavor of menthol and both are of non-combusted product format (carbon heat source). As I further explained in the chemistry review (see section 4.1), the increase in menthol 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 social science perspective.

4.5. BEHAVIORAL AND CLINICAL PHARMACOLOGY

Behavioral and clinical pharmacology reviews were completed by Theresa Carbonaro on October 25, 2017 and February 12, 2018.

The final behavioral and clinical pharmacology review concludes that the new tobacco product has different characteristics which affect addiction compared to the predicate tobacco product,

[5] Analytes and relative decreases under the ISO smoking regimen reported by the applicant include: acetaldehyde (↓67%), acrolein (↓71%), acetone (↓75%), crotonaldehyde (↓75%), propionaldehyde (↓69%), methyl ethyl ketone (↓67%). The analytes that are reported to be below the limit of quantitation 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.

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

- 18% decrease in nicotine content (mg/cig)
- 77% decrease in nicotine smoke yield (ISO smoking regimen)
- 64% decrease in nicotine smoke yield (CI smoking regimen)

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 the nicotine content in both the new and predicate tobacco products is above the "addictive threshold," does not factor into FDA's review, which is focused on whether there are differences in characteristics between the new and predicate tobacco products that cause the new tobacco product to raise different questions of public health. The applicant provided nicotine smoke yield data under ISO and CI smoking regimens, and nicotine yields were lower in the new tobacco product compared to the predicate tobacco product. Given that nicotine is an addictive substance, 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 behavioral and clinical pharmacology perspective.

5. ENVIRONMENTAL DECISION

An environmental review was completed by Ronald Edwards 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:

- Differences in tobacco:
  - 15% decrease in total amount of tobacco
  - Removal of tobacco from the heat source assembly (HSA) heat source
  - Change from (b) (4) [redacted] to (b) (4) [redacted] in the tobacco substrate (SUB) section
  - Change in tobacco blend in the tobacco roll rod (TBR), including the removal of (b) (4) [redacted]
- Differences in non-tobacco ingredients:
  - 13% increase in menthol
  - Addition of two complex flavor ingredients ((b) (4) [redacted])
  - Removal of three complex flavor ingredients ((b) (4) [redacted])
  - Change in OFP tipping paper from paper/foil/paper laminate to paper

  - Change in FEP overwrap from paper to paper/foil/paper laminate
- Differences in HPHCs:
  - 119% increase in formaldehyde smoke yield (ISO smoking regimen)
  - 1% decrease in formaldehyde smoke yield (CI smoking regimen)
  - 67-75% decrease in acetaldehyde, acrolein, acetone, crotonaldehyde, propionaldehyde, and methyl ethyl ketone (ISO smoking regimen)
  - 30-67% decrease in acetaldehyde, acrolein, acetone, crotonaldehyde, propionaldehyde, and methyl ethyl ketone (CI smoking regimen)
  - 18% decrease in nicotine content (mg/cig)
  - 77% decrease in nicotine smoke yield (ISO smoking regimen)
  - 64% decrease in nicotine smoke yield (CI smoking regimen)
- Differences in design parameters:
  - 32% increase in cigarette draw resistance
  - 32% decrease in pack moisture
  - 5% decrease in SUB tobacco filler mass
  - 20% decrease in TBR tobacco filler mass
  - 54% increase in SUB tobacco rod density
  - 14% decrease in TBR tobacco rod density
  - 38% decrease in SUB length
  - 8% decrease in TBR length
  - 15% increase in HSA cigarette paper base paper porosity
- Incorporation of a functional filter, which includes the following changes to the filter design:
  - 110% increase in total filter length
  - 22% decrease in total denier (hollow segment)
  - 52% increase in denier per filament (hollow segment)
  - 14% decrease in filter density
  - Increase in pressure drop
  - 14% increase in tipping paper length

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health. The removal of tobacco from the HSA heat source and the changes in tobacco blends in the SUB and TBR sections do not cause the new tobacco product to raise different questions of public health. These types of changes could lead to increases in HPHCs, especially B[a]P. The applicant provided smoke yields for B[a]P and 19 other HPHCs under both ISO and CI smoking regimens that show that all HPHC levels were the same or lower in the new tobacco product, except for one (formaldehyde under ISO conditions). Based on the totality of the data, the increase in formaldehyde ISO yields does not cause the new tobacco product to raise different questions of public health. Similarly, the HPHC data demonstrate that the differences in complex flavor ingredients between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. The applicant provided nicotine content and smoke yield data under ISO and CI smoking regimens. Nicotine content and smoke yields were lower in the new tobacco product compared to the predicate tobacco product. Given that nicotine is an addictive substance, 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. Although there is a 13% increase in the amount of menthol added to the new tobacco product, I note that the menthol levels in both products exceed the reported threshold limit needed

to impart sensory effects and fall within the lower range of menthol levels measured in a survey of commercial mentholated cigarettes (2.9 to 19.6 mg/cig).[6,7] Furthermore, although the new tobacco product has a different target value and wider range specification than the predicate tobacco product for added menthol, the upper range of menthol added to the predicate tobacco product encompasses the new tobacco product target value and the lower range of menthol added to the new tobacco product encompasses the predicate tobacco product target value. The menthol range for the new tobacco product, while wider than that of the predicate tobacco product, is not overly broad. Therefore, the difference in menthol levels between the new and predicate tobacco products does not cause the new tobacco product to raise different questions of public health.

The design parameter changes to the cigarette draw resistance, SUB tobacco filler mass, TBR tobacco filler mass, SUB tobacco rod density, TBR tobacco rod density, cigarette paper base paper porosity, filter total denier, denier per filament, filter density, total filter length, and filter pressure drop each tend to decrease smoke constituent yields and, thus, do not cause the new tobacco product to raise different questions of public health. TNCO testing confirms that the new tobacco product has reduced TNCO yields compared to the predicate tobacco product. The changes to structural wraps and papers do not impact smoke HPHC yields. Since the new tobacco product is not combusted, glycerin rather than moisture generally affects aerosol yields, and the decrease in pack moisture does not cause the new tobacco product to raise different questions of public health. The changes in the SUB, TBR, and filter segment lengths occurred due to incorporation of a functional filter in the new tobacco product. The filter segment of the new tobacco product has a pressure drop and provides aerosol filtration. The addition of such a filter is expected to reduce the levels of HPHCs in smoke and, indeed, the submitted data generally support this. 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 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).

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 an 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.

An SE order letter should be issued for the new tobacco product in SE0014221, as identified on the cover page of this review.

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[6] Ai, J.; Taylor, K.M.; Lisko, J.G.; Tran, H.; Watson, C.H.; and Holman, M.R. Menthol Content in US Marketed Cigarettes. *Nicotine Tob Res*. 2016;18(7):1575-80.

[7] Menthol levels were measured in whole combustible cigarettes; however, the methods used to obtain these data did not include combustion of the samples. Based on the product design characteristics of Eclipse Menthol, this conclusion does not differ from that of the combustible cigarettes utilized for this method.