FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0013711

SE0013711: Marlboro Box	
Package Type	Hard Pack
Package Quantity	20 Cigarettes
Length	79 mm
Diameter	7.89 mm
Ventilation	12%
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	Philip Morris USA Inc.
Report Type	Regular
Product Category	Cigarette
Product Sub-Category	Combusted Filtered
Recommendation	
Issue a Substantially Equivalent (SE) order.	

Technical Project Lead (TPL):

Matthew J. Walters -S
2018.08.10 07:34:08 -04'00'

Matthew J. Walters, Ph.D., MPH
CDR, U.S. Public Health Service
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: 2018.08.10 07:47:06 -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:

SE0013711: Marlboro Box	
Product Name	Marlboro Box (2007)
Package Type	Hard Pack
Package Quantity	20 Cigarettes
Length	79 mm
Diameter	7.89 mm
Ventilation	12%
Characterizing Flavor	None

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

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On September 23, 2016, FDA received one SE Report (SE0013711) from Altria Client Services (ALCS) on behalf of Philip Morris USA Inc. (PM USA). FDA acknowledged the SE Report on September 26, 2016. FDA issued an Advice/Information Request (A/I) letter on June 7, 2017. FDA received a response (SE0014230) to the A/I letter on August 4, 2017. FDA issued a Preliminary Finding (PFind) letter on October 26, 2017. A response to the PFind letter was due to FDA by November 25, 2017. The response was submitted via CTP Electronic Submission Gateway (ESG) on November 21, 2017. However, due to technical issues with CTP systems, FDA did not receive the response to the PFind letter by the due date of November 25, 2017. On November 30, 2017, FDA requested the applicant resubmit its response to the October 26, 2017, PFind letter. FDA received the response (SE0014422) on November 30, 2017, and reviewed it during the current review cycle. On December 15, 2017, FDA conducted a teleconference requesting the applicant confirm the Tobacco Product Master File (TPMF) submission tracking numbers (STNs) referenced in their response to the PFind letter. On December 15, 2017, FDA received an amendment (SE0014432) containing the requested information. FDA issued an A/I letter on April 19, 2018. FDA received a response (SE0014721) to the A/I letter on May 14, 2018.

Product Name	SE Report	Amendments
Marlboro Box	SE0013711	SE0014230 SE0014422 SE0014432 SE0014721

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 Gouri Chattopadhyay on September 26, 2016, and by Maria Suarez on April 19, 2018.

The final review concludes that this 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 October 14, 2016, 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.[1]

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 review dated July 31, 2018, concludes 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 Delshanee Kotandeniya on November 21, 2016, September 21, 2017, and March 6, 2018.[2]

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:

- Decrease in (b) (4) (2%), (b) (4) (2%), and (b) (4) (1%) tobacco

[1] An addendum to this existing OCE review memorandum was completed on February 14, 2018, to (1) identify the predicate tobacco product as "Marlboro Box;" (2) identify the characterizing flavor associated with the predicate tobacco product; (3) correct the field "Company's Name;" and (4) modify the "Correspondence and Supporting Documents" section. The addendum review does not change the conclusion of the initial determination that the predicate product has grandfathered status.

[2] Two (b) (4)) were referenced in the original SE Report and reviewed as part of the final March 6, 2018, chemistry review.

- Increase in (b) (4) (4%)
- Increase in (b) (4) (4%) in the cigarette paper
- Addition of (b) (4) mg/g (b) (4) to the cigarette paper
- Addition of (b) (4) mg/g (b) (4) to the tipping paper
- Increase in (b) (4) (4%) in the filter plug wrap
- Removal of (b) (4) from the tipping paper
- Increase in (b) (4) (492%) in the tipping paper
- Addition of (b) (4) µg/g (b) (4) to the tipping paper

The review concludes that 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 based on HPHC data for the new and surrogate predicate products: TNCO, NNN, NNK, acetaldehyde, acrolein, benzene, and formaldehyde under both the ISO and CI regimens. The review discusses HPHC data for a 2016 surrogate predicate product,[3] citing TPMFs[4] containing Labstat and Enthalpy Lab analytical methods as well as findings from (b) (4) related to the 2016 surrogate predicate product. The review also discusses HPHC data for a 2017 surrogate predicate product.[6] As the TPL, I find that for this SE Report, HPHC data for the 2017 surrogate predicate product is more reliable than the HPHC data for the 2016 surrogate predicate product because data for the new and 2016 surrogate predicate products were not generated in the same laboratory at the same time, limiting FDA's ability to sufficiently compare the HPHC data. In contrast, the new and 2017 surrogate predicate products were manufactured in 2017 and HPHC data was generated in July 2017 in the same ALCS laboratory for both products. Therefore, the data for the new and 2017 surrogate predicate products are more reliable because they were measured in the same laboratory and at the same time which limited the variability in the HPHC data and analysis. Because HPHC data for the 2016 surrogate predicate product is not necessary to the determination of substantial equivalence for this SE Report, information in the TPMFs and findings from (b) (4) related to this surrogate predicate product, as cited by the chemistry reviewer, are also not necessary for a SE determination for this SE Report. The information submitted relating to analytical methods used to generate HPHC data for the new and 2017 surrogate predicate products (Table 6 in the chemistry review) is adequate. The chemistry review cites ALCS SOPs for the HPHC testing of the new and 2017 surrogate predicate products as well as ISO accreditation for the ALCS laboratory conducting the HPHC testing, to conclude that it is sufficient to rely on the HPHC data for the new and 2017 surrogate predicate products. Furthermore, TOST[7] calculations demonstrate that the HPHC yields for the new and 2017 surrogate predicate products are analytically equivalent under ISO and CI smoking regimens. Therefore, the differences in characteristics between the new and predicate tobacco products

[3] This product is the remanufactured predicate product in 2016 because the actual predicate tobacco product was no longer available for testing. Accordingly, data from the 2016 surrogate predicate product can be extrapolated to the predicate product.
[4] Tobacco Product Master Files
[5] FDA issued an NSE order for (b) (4) in June 2015 based on the addition of (b) (4) in the monogram ink. SE0013711 states that the new product in this SE Report is identical to the new product in (b) (4) except that (b) (4) is not included in the monogram ink.
[6] This product is the predicate product re-created in 2017 because the actual predicate tobacco product was no longer available for testing. Accordingly, data from the 2017 surrogate predicate product can be extrapolated to the predicate product.
[7] Two One-Sided t-Test

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 Komal Ahuja on November 18, 2016, and by Yan Sun on September 22, 2017, and January 19, 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 related to product engineering:

- Puff count was increased by 5%
- Band porosity was decreased by 56%
- Band width was increased by 9%

The applicant indicated that the puff count in the new product compared to the predicate product was increased by less than one puff and the band width was increased by 9% from the predicate product to the new product. In addition, the band porosity target value of the new product was found to be 56% less than the band porosity target value of the predicate product. The applicant provided the total weighted cigarette paper porosity, which is 4% less than that of the predicate product. A decrease in porosity may increase smoke constituents, however, TNCO yields for the new product are comparable or decreased to those of the predicate product. The applicant provided data from 2016 and 2017 surrogate predicate products because the predicate tobacco product was no longer available for testing, and that data can be extrapolated to the predicate 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. TOXICOLOGY

Toxicology reviews were completed by Sheila Healy on May 24, 2017, Maocheng Yang on September 29, 2017, and Shaji Theodore on January 17, 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 increases in HPHC data for the new and 2017 surrogate predicate products. The review cites TOST calculations demonstrating that the HPHC yields for the new and 2017 surrogate predicate products are analytically equivalent under ISO and CI smoking regimens. 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.

5. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on August 9, 2018. The FONSI was supported by an environmental assessment prepared by FDA on August 9, 2018.

6. CONCLUSION AND RECOMMENDATION

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

- Decrease in (b) (4) (2%), (b) (4) (2%), and (b) (4) (1%) tobacco
- Increase in (b) (4) (4%)
- Increase in (b) (4) (4%) in the cigarette paper
- Addition of (b) (4) mg/g (b) (4) to the cigarette paper
- Addition of (b) (4) mg/g (b) (4) to the tipping paper
- Increase in (b) (4) (4%) in the filter plug wrap
- Removal of (b) (4) from the tipping paper
- Increase in (b) (4) (492%) in the tipping paper
- Addition of (b) (4) µg/g Pigment Red 101 to the tipping paper
- Puff count was increased by 5%
- Band porosity was decreased by 56%
- Band width was increased by 9%
- Increases in HPHC yields under ISO and CI smoking regiments

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 had minimal changes in the tobacco blends and ingredients, with the most noteworthy difference in the tobacco blend being an increase in (b) (4) (4%). In addition, the new product compared to the predicate product had a number of increases in ingredients; however, these differences were not analytically significant. The applicant provided HPHC yields for new and 2017 surrogate predicate products under ISO and CI smoking regimens: TNCO, acetaldehyde, formaldehyde, acrolein, benzene, NNK, and NNN. The applicant provides ALCS SOPs for the HPHC testing of the new and 2017 surrogate predicate products as well as ISO accreditation for the ALCS laboratory. This information demonstrates it is sufficient to rely on the HPHC data for the new and 2017 surrogate predicate products. Furthermore, TOST calculations demonstrate that the HPHC yields for the new and 2017 surrogate predicate products are analytically equivalent under ISO and CI smoking regimens. 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 is a grandfathered product (i.e., was commercially marketed in the United States other than 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 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 the 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 SE0013711, as identified on the cover page of this review.