U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0006275

SE0006275: Natural American Spirit Balanced Taste	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter[1]	7.89 mm
Ventilation	34%
Characterizing Flavor	None
Attributes of SE Report	
Applicant	Santa Fe Natural Tobacco Company, Inc.
Report Type	Provisional
Product Category	Cigarettes
Product Sub-Category	Combusted, Filtered
Recommendation	
Issue a Substantially Equivalent (SE) order.	

[1] The applicant submitted the circumference which allowed for a calculation of diameter

Technical Project Lead (TPL):

Digitally signed by Melissa Mcculloch -S
Date: 2018.10.19 15:12:55 -04'00'

Melissa McCulloch, Ph.D.
Senior Regulatory Scientist
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: 2018.10.22 06:14:51 -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:

SE0006275: Natural American Spirit Balanced Taste	
Product Name	Natural American Spirit Medium Taste
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	84 mm
Diameter[1]	7.89 mm
Ventilation	32%
Characterizing Flavor	None

The predicate tobacco product is a combusted filtered cigarette manufactured by the applicant. It should be noted that the applicant identified two predicate tobacco products for this SE Report: Natural American Spirit Medium Taste and Camel Filters Hard Pack prior to the start of the scientific review. On February 26, 2016, the applicant withdrew Camel Filters Hard Pack as a predicate tobacco product (amendment SE0012984).

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

FDA received an SE Report from R.J. Reynolds Tobacco Company (RJRT) on behalf of Santa Fe Natural Tobacco Company, Inc. on March 22, 2011 and issued an Acknowledgment letter on March 25, 2013. On March 21, 2013, FDA received an amendment (SE0007894) from the applicant to request additional time to respond to the anticipated[2] Advice/Information Request (A/I) letter for this SE Report. FDA issued an A/I letter on March 25, 2013 for this SE Report. On April 1, April 5, April 9, and April 11, 2013, FDA conducted 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 the applicant's timeline and proposal to amend the SE Report (SE0008212). FDA issued an Extension Response letter on April 17, 2013 requesting the applicant submit a complete response to the A/I letter and any additional information prior to the start of scientific review[3] of the SE Report. FDA issued a Public Health Impact (PHI) A/I letter on May 10, 2013. On July 9, 2013, FDA received the applicant's response to the PHI A/I letter (SE0009215), and this SE Report was assigned to Tier 1. On October 10, 2014, FDA issued a Notification letter, indicating that scientific review was expected to begin on November 25, 2014. On November 21, 2014, FDA received an amendment (SE0010760) containing a revised SE Report. On February 4, 2015, FDA received an unsolicited amendment (SE0010852) containing clarification to inaccuracies found in the ingredient list within this SE Report. FDA issued an A/I letter on July 10, 2015 and received the applicant's response on September 8, 2015 (SE0012359). FDA issued another A/I letter on

[2] The applicant had received A/I letters for other SE Reports not subject to this review. In anticipation of receipt of a similar A/I letter for the SE Report subject of this review, RAIS proactively requested an extension of time.

[3] FDA stated in this letter that, at a later date, it would issue a Notification letter notifying RAI Services Company of the projected scientific review start date of the SE Report.

December 28, 2015 which included a correction to one of the deficiencies in the July 10, 2015, A/I letter. On January 5, 2016, January 12, 2016, and January 19, 2016, teleconferences were held to discuss procedures for withdrawing a predicate tobacco product for this SE Report. The applicant submitted an amendment on February 26, 2016 (SE0012984). On October 3, 2016, FDA issued a Preliminary Finding (PFind) letter to the applicant and received a response on November 2, 2016 (SE0013736).

Product Name	SE Report	Amendments
Natural American Spirit Balanced Taste	SE0006275	SE0007894 SE0008212 SE0009215 SE0010760 SE0010852 SE0012359 SE0012984 SE0013736

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 and by Barbara Banchero on August 21, 2018.

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

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews 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 January 9, 2015[4], 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] OCE completed a grandfathered review on January 9, 2015 prior to the withdrawal of the predicate tobacco product "Camel Filters Hard Pack."

4.1. CHEMISTRY

Chemistry reviews were completed by Christina Young on March 18, 2015, November 9, 2015, and April 11, 2016 and by Sharyn Miller on December 23, 2016.

The final chemistry review concludes that the new tobacco product has different characteristics related to product chemistry compared to the predicate tobacco product and that the SE Report lacks adequate evidence to demonstrate that the differences do not cause the new tobacco product to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. Your SE Report provides aromatic amine method sensitivity in your November 2016 amendment. You stated that the LOD signal to noise acceptance criteria is 3:1, but you did not provide LOD signal to noise ratios. Without the LOD signal to noise ratios, we cannot fully evaluate 4-aminobiphenyl method sensitivity. Provide the LOD signal to noise data for the 4-aminobiphenyl analytical method.

2. Your SE Report provides ion ratio data and ion ratio acceptance criteria for determining aromatic amine method selectivity in your November 2016 amendment. However, the information you provided is inadequate. Provide the following information so we can fully evaluate your 4-aminobiphenyl method selectivity:

    a. In an addendum to the validation report dated June 26, 2014, you acknowledged ion selection discrepancies from the original validation ion ratio experiment. To address these concerns, you conducted a subsequent set of ion ratio experiments using non-reference cigarettes under ISO and Canadian Intense (CI) smoking regimens. However, given the unique physical and chemical characteristics of the cigarettes examined, the use of non-reference cigarettes is inappropriate for analytical method validation studies. Provide ion ratio comparison data between standards and reference cigarettes under ISO and CI smoking regimens for 4-aminobiphenyl.

    b. The acceptance criteria require a method blank not containing any analyte above 50% LOQ at standard level 1. With three analytical runs used for blank response validation, conducted on three different days (3-5-13, 3-6-13, and 3-7-13), it is unclear why you only provided 50% of LOQ response from one run (3-5-13). Given the potential for day-to-day system variability, the method blank response should be compared to the 50% of LOQ response (standard level 1) within the same run. Provide the 50% of LOQ responses for the two runs conducted on 3-6-13 and 3-7-13.

    c. The acceptance criteria also require that the mean analyte ion ratios in standard and authentic matrix samples must agree within ± 75%. It is unclear how you established this threshold given that it was set nearly 4-fold higher than the observed highest ion ratio percent difference of approximately 19%. Potential chromatogram interferences in the primary ion channel may distort the true peak area by either enhancing or suppressing the signal. As a result, the analyte concentration may not reflect the true concentration in the sample.

Interferences can be observed in the analyte ion ratio calculation using the area of the primary to secondary ion for each analyte. Establishing a ±75% ion ratio acceptance criterion between unknowns and standards disregards the potential interference effects on analyte quantification. Provide scientific rationale and evidence regarding how you developed the ±75% ion ratio acceptance criteria and justify how the ±75% ion ratio difference between standards and samples does not raise concerns regarding method selectivity.

3. Your SE Report includes HPHC quantities for NNN in mainstream smoke (MSS) under both the ISO and CI smoking regimens for the new product and remanufactured predicate product. To address the NNN data variability, you compared tobacco filler NNN content and NNN mainstream smoke yields over 16 new product manufacturing runs using ISO and CI smoking regimens. However, you did not provide the corresponding filler-to-smoke NNN correlation data for the predicate product. Provide scientific evidence to justify the wide MSS NNN data variability for the predicate product.

4. Your SE Report provides analyte ion ratio determination for aromatic amines in your November 2016 amendment. It is unclear why you used different standard levels for 4-aminobiphenyl ion ratio determination. For example, you compared the sample ion ratios to ion ratios in standard levels 1 and 2 for 4-aminobiphenyl, but compared the ion ratios in standard levels 4 through 8 for 1-aminonapthalene and 2-aminonapthalene. Provide scientific rationale and evidence for the use of different standard levels in determining aromatic amine ion ratios. FDA needs this information to fully evaluate your 4-aminobiphenyl method validation selectivity.

5. Your SE Report provides the aromatic amine ion ratio comparison data between standards and non-reference cigarettes in your November 2016 amendment. The information provided in the ion ratio summary and the supporting ion ratio data tables is inconsistent. The summary section in Appendix 205 of the November 2016 amendment states that Table 3 shows the ion ratios for 1-aminonapthalene and 2-aminonapthalene smoked under ISO and CI smoking regimens using standard levels 4 through 8. However, in Table 3, the analyte columns reflect 3-aminobiphenyl and 4-aminobiphenyl and not 1-aminonapthalene and 2-aminonapthalene. Provide an explanation for this inconsistency.

Therefore, the review concludes that the applicant did not demonstrate 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. However, as TPL, I conclude that the above five deficiencies were identified in error. A detailed discussion for each of the five deficiencies follows below.

Deficiency 1 above concerns the limit of detection (LOD) and states that complete data for the signal to noise (S/N) ratios was not provided for the analytical method used to measure aromatic amines. However, the applicant provided sufficient information to establish that the limit of quantitation (LOQ) was reliable for this method. The LOQ is the lowest value of the analyte that the can be determined by the method with acceptable accuracy and precision. In this instance, the LOD for this method does not provide meaningful information regarding the

analytical performance of this method. Although the information for the LOD was incomplete, since there are no concerns with the LOQ, the lack of LOD information does not raise concerns regarding the reliability of the data provided in this SE Report. Therefore, Deficiency 1 should not be communicated to the applicant.

Deficiencies 2, 4 and 5 above relate to the selectivity of the analytical method for aromatic amines used to measure 4-aminobiphenyl. Selectivity is the ability to explicitly distinguish and evaluate an analyte in the presence of all components that can interfere with the accurate measurement of the analyte. Method accuracy is the extent to which the test results agree with the true value of the analyte. The applicant provided method validation data to establish 4-aminobiphenyl accuracy using low and high level spike/recovery samples. All method validation spike/recovery sample values for 4-aminobiphenyl were within the applicant's acceptance criteria for the method. Consequently, the applicant has provided sufficient information to establish that this method can accurately measure 4-aminobiphenyl. In this instance, information regarding selectivity for this method is not necessary because the applicant has demonstrated that the method is able to accurately measure the analyte in the presence of any potential interference. Since there are no concerns related to this method being able to accurately measure 4-aminobiphenyl, Deficiencies 2, 4 and 5 should not be communicated to the applicant.

Deficiency 3 above concerns the applicant's approach to describe variability in the NNN data submitted. Based on the information provided by the applicant, there is 16% higher NNN in the mainstream smoke (MSS) for the new tobacco product (20.9 ng/cig) compared to the predicate tobacco product (18.0 ng/cig) using the Canadian Intense (CI) smoking regimen. Although there is a 16% increase in NNN in the MSS of the new tobacco product compared with the predicate tobacco product, the amount of NNN in the new and predicate product is very small. Further, the reported LOQ for NNN is approximately 7 ng/cig[5], a measurement of approximately 20 ng/cig is at the low end of the quantitation range and the measurement is expected to include high variability. The 16% increase in NNN for the new tobacco product compared to the predicate tobacco product is within the expected variability of the analytical method, therefore the amount of NNN in the new tobacco product does not cause the new product to raise different questions of public health. Therefore, deficiency 3 should not be communicated to the applicant.

The final chemistry review does not discuss the differences in tobacco blend or the (b) (4) increase in tipping glue between the new and predicate tobacco products. However, these differences are evaluated in earlier chemistry reviews. The new tobacco product contains (b) (4) less tobacco than the predicate tobacco product. Further, there is (b) (4) less flue cured lamina and (b) (4) more oriental lamina in the new tobacco product compared to the predicate tobacco product. Differences in tobacco blend may result in different HPHC profiles. The (b) (4) increase in oriental lamina tobacco in the new tobacco product correlates to an absolute amount of (b) (4) which contributes less than (b) (4) to the overall tobacco mass in the new tobacco product and does not affect the MSS smoke yields of HPHCs in this case. Therefore, the differences in tobacco blend between the new and predicate tobacco products do not

[5] Oldham, M.J., DeSoi, D.J., Rimmer, L.T., Wagner, K.A., Morton, M.J. (2014). *Regulatory Toxicology and Pharmacology*, 70 (1), 138-148, https://doi.org/10.1016/j.yrtph.2014.06.017.

cause the new tobacco product to raise different questions of public health from a chemistry perspective. With respect to the (b) (4) increase in tipping glue, the applicant states that the filter segment is longer in the new tobacco product and this also leads to greater surface area that is covered by tipping glue. HPHCs in MSS are not likely to be affected since tipping glue is not combusted. Consequently, for the purposes of this review, the higher quantity of this non-tobacco ingredient does not cause the new tobacco product to raise different questions of public health. Further discussion of this information and the potential risk of the differences in the quantities of this non-tobacco ingredient to public health are included in Toxicology section 4.3.

No chemistry deficiencies remain. Therefore, I find 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.

4.2. ENGINEERING

Engineering review was completed by James Melchiors on March 16, 2015, November 3, 2015, April 25, 2016 and December 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 between the new and predicate tobacco products:

- A different filter rod that includes a longer white filter segment and different tow parameters
- A different cigarette paper that includes a lower base paper basis weight and narrower bands
- Differences in the tobacco blend

With respect to the differences in filter rod; the filter length increases by 9.5%, the filter density increases by 8.6%, and the filter pressure drop increases by 9.2% from the predicate to the new tobacco product. Also, the denier per filament increases by 28.6% and the total denier increases by 9.4% for the white filter segment from the predicate to the new tobacco product. Finally, the denier per filament decreases by 23.1%, the total denier increases by 33.3%, and the charcoal loading increases by 6.3% for the charcoal filter segment from predicate to the new tobacco product. Except for the increase in denier per filament for the white filter segment, when reviewed individually, these differences would be expected to reduce smoke constituent yields and therefore do not cause the new tobacco product to raise different questions of public health. Furthermore, the differences can be reviewed in total by comparing the tar, nicotine, and carbon monoxide (TNCO) yields of the new and predicate tobacco products. The TNCO values are comparable between the new and predicate tobacco products. Therefore, the differences between the filters, including the increase in denier per filament, in the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health from an engineering perspective.

The cigarette paper base paper basis weight target specification for the new tobacco product is 10% lower compared to the predicate tobacco product. Cigarette paper base paper basis weight can impact the tobacco product's puff count. In this SE Report, the puff count increased by 10% in the new tobacco product compared to the predicate tobacco product. An increased puff count can lead to higher smoke constituent yields. However, the TNCO values are comparable between the new and predicate tobacco products. Therefore, the differences between the cigarette paper base paper basis weight in the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health from an engineering perspective.

Tobacco blend differences are evaluated in the chemistry review and discussed in Chemistry section 4.1 of this review.

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 Susan M. Chemerynski on June 26, 2015, Casandra Cartagena on August 23, 2016 and Ying Bryant on June 27, 2018.

The final toxicology review concludes that the new tobacco product has different characteristics related to product toxicity compared to the predicate tobacco product and that the SE Report lacks adequate evidence to demonstrate that the differences do not cause the new tobacco product to raise different questions of public health. The review identifies the following deficiency that has *not* been adequately resolved:

1. Your SE Report provided new supplemental HPHC smoke yield data for benzene, 1,3-butadiene, isoprene, NNN, and toluene from the new and predicate products that were generated within similar timeframes (between Q3 2015 and Q2 2016). In this analysis, NNN smoke level is increased 16% in the new product when compared to the predicate product under the Canadian Intense smoking regimen. NNN is classified as a human carcinogen by IARC. You did not explain why such an increase in NNN level does not cause the new product to raise different questions of public health. In addition, a statistical evaluation of the new data indicates following concerns related to the data analysis:

    a. You applied superiority tests (that is the use of *p*-values) to evaluate similarity or difference in HPHC levels between the new and predicate products. However, it is not a recommended statistical practice to use insignificant *p*-values to accept the null hypothesis of no difference in HPHC levels between two products. You need to provide datasets with larger sample sizes and reduce the total variability for both new and predicate products, particularly the between manufacturing run variability. Additionally, you may consider an equivalence test approach to establish whether HPHC levels are similar between the new and predicate products.

b. You used a fraction of the data (within the period of Q3 2015 and Q2 2016) from the new product for comparing temporally matched HPHC levels between the new and predicate products. However, the use of temporally matched data for analyses may not necessarily reflect the characteristics of the two products over time. Additionally, the analyses comparing the data from two periods (before and after Q3 2015) for the new product reveal large differences in HPHC levels. It raises concern that an implicit assumption was made in the evaluation of temporally matched data. Therefore, sufficient multiple manufacturing runs are needed for both new and predicate products to incorporate the variability among manufacturing runs into the evaluation of product similarity.

Provide scientific rationale and evidence why the increase in NNN level in the new data analysis does not cause the new product to raise different questions of public health.

Therefore, the review concludes that the applicant did not demonstrate 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 toxicology perspective. However, as TPL, I conclude that the above deficiency was identified in error.

The deficiency outlined above concerns the applicant's approach to describe variability in the NNN data submitted. As discussed with respect to Chemistry deficiency 3 in section 4.1 of this review, based on the information provided by the applicant, there is 16% higher NNN in the MSS for the new tobacco product compared to the predicate tobacco product using a CI smoking regimen. However, based on the expected variability in measurement of this low amount of NNN in both the new and predicate tobacco products, the 16% higher amount of NNN in the new tobacco product compared to the predicate tobacco product should not have been deferred to toxicology because this difference is within the expected analytical variability for this measurement. The amount of NNN reported for the new tobacco product compared to the predicate tobacco product does not cause the new tobacco product to raise different questions of public health. Therefore, this deficiency should not be communicated to the applicant.

The final toxicology review does not discuss the 26% increase in tipping glue between the new and predicate tobacco products. However, this increase is evaluated in earlier cycles of chemistry and toxicology reviews. The applicant states that the filter segment is longer in the new tobacco product and this leads to greater surface area that is covered by tipping glue. The toxicology review determined that most ingredients in the tipping glue are present in small quantities (<0.2 mg/cig), making it unlikely that there would be an increased risk from dermal exposure in the new tobacco product. One exception is polyvinyl acetate ethylene copolymer which after the 26% increase is 6.32 mg/cig in the new tobacco product. Since the tipping glue is not expected to be combusted, volatilized, or otherwise released during normal cigarette consumption, consumer exposure to chemical constituents by the inhalation route while smoking is not expected. As the tipping glue is below the paper, it is unlikely to come into direct dermal contact with the skin. Therefore, the differences in tipping glue between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

No toxicology deficiency remains. Therefore, I find 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.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act for this provisional SE Report (SE0006275) 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:

- A different filter rod that includes a longer white filter segment and different tow parameters
  - Filter length increases by 9.5%
  - Filter density increases by 8.6%
  - Filter pressure drop increases by 9.2%
  - Denier per filament increases by 28.6%
  - Total denier increases by 9.4% for the white filter segment
  - Denier per filament decreases by 23.1%, the total denier increases by 33.3%, and the charcoal loading increases by 6.3% for the charcoal filter segment
- A different cigarette paper that includes a lower base paper basis weight and narrower bands
  - Base paper basis weight target specification is 10% lower
- Differences in the tobacco blend
  - (b) (4) less overall tobacco
  - (b) (4) less flue cured lamina
  - (b) (4) more oriental lamina
- A (b) (4) increase in the amount of tipping glue

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco product to raise different questions of public health.

The differences in filter rod and cigarette paper were evaluated by comparing the TNCO yields of the new and predicate tobacco products, which did not demonstrate any significant differences. The (b) (4) increase in oriental lamina tobacco in the new tobacco product correlates to an absolute amount of (b) (4), which contributes less than (b) (4) to the overall tobacco mass in the new tobacco product and does not affect the MSS smoke yields of HPHCs in this case. With respect to the (b) (4) increase in tipping glue, most ingredients in the tipping glue are present in small quantities (<0.2 mg/cig), making it unlikely that there would be an increased risk from

dermal exposure in the new tobacco product. Additionally, tipping glue is not expected to be combusted, volatilized, or otherwise released during normal cigarette consumption; consumer exposure to chemical constituents by the inhalation route while smoking is not expected. Therefore, the differences in filter rod, cigarette paper, tobacco blend and tipping glue 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., were 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 SE0006275, as identified on the cover page of this review.