FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0006259 and SE0006260

SE0006259: Salem Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	13%
Characterizing Flavor	Menthol
SE0006260: Salem Slim 100's Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.35 mm
Ventilation	47%
Characterizing Flavor	Menthol
Common Attributes of SE Reports	
Applicant	ITG Brands, LLC
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Combusted Filtered
Recommendation	
Issue Not Substantially Equivalent (NSE) orders.	

Technical Project Lead (TPL):

Matthew J. Walters -S
2018.07.31 08:49:55 -04'00'

Matthew Walters, Ph.D., MPH
CDR, US Public Health Service
Deputy 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: 2018.07.31 08:53:05 -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 products:

SE0006259: Salem Box	
Product Name	Kool Filter Kings Box
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	10%
Characterizing Flavor	Menthol
SE0006260: Salem Slim 100's Box	
Product Name	Salem Lights Green Label Box
Package Type	Box
Package Quantity	20 cigarettes
Length	98 mm
Diameter	7.20 mm
Ventilation	47%
Characterizing Flavor	Menthol

The predicate tobacco products are combusted filtered cigarettes manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

FDA received two SE Reports (SE0006259 and SE0006260) on March 22, 2011, from R.J. Reynolds Tobacco Company (RJRT). On February 26, 2013, a Public Health Impact (PHI) review was completed, assigning these SE Reports to PHI Tier 1. On March 21, 2013, FDA received an amendment (SE0007894) requesting an extension to respond to Advice/Information Request (A/I) letters that were issued to other SE Reports not subject of this TPL review. [1] FDA issued A/I letters for the referenced SE Reports on March 25, 2013. On April 5, 2013, FDA held a teleconference with the applicant to clarify the amount of time needed for the extension request, and the applicant requested an extension of 4 months. On April 9, 2013, FDA held another teleconference with the applicant to request the applicant to submit a proposal to FDA on how the applicant would utilize the 4-month extension to provide response to the A/I letters. On April 11, 2013, FDA received an amendment (SE0008212) to recap discussions held in the teleconferences regarding the proposed timeline to submit information requested in the A/I letters. On April 17, 2013, FDA issued a letter responding the applicant's extension request to

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

inform the applicant to provide a complete response to all issues stated the A/I letters and submit additional information before the start of the scientific review of the SE Reports. The letter also explained that the applicant would be notified of the start of the scientific review via a Notification letter. FDA issued a (PHI) A/I Request letter on May 10, 2013. On June 7, 2013, FDA received amendments (SE0008881 and SE0008917) in response to the PHI A/I Request letter. On July 1, 2013, a second PHI review was completed, assigning these SE Reports to PHI Tier 2. On June 11, 2015, FDA received an unsolicited amendment (SE0011977) to amend the original SE Report for SE0006259. FDA issued a Notification letter on June 11, 2015, stating that scientific review of the SE Reports was expected to begin on July 26, 2015. On June 25, 2015 FDA received an amendment (SE0012011) requesting an 11-day extension to the response date stipulated in the Notification letter. On June 29, 2015, FDA received an amendment (SE0012014) informing the FDA of the transfer of ownership for SE0006259 and SE0006260 to ITG Brands, LLC (ITGB) as well as requesting an 11-day extension to respond to the Notification letter. On July 1, 2015, FDA received a general correspondence (TC0001328) informing FDA of the transfer of ownership to ITGB. FDA issued an Extension Denied letter on July 1, 2015. On July 7, 2015, FDA received an unsolicited amendment (SE0012167) requesting clarification and confirmation of the scientific review start date for the SE Reports. On July 8, 2015, FDA received an unsolicited amendment (SE0012168) correcting submission tracking numbers in amendment SE0012167. On July 10, 2015, FDA issued a Correction letter to correct and clarify the scientific review start date provided in the July 1, 2015, Extension Denied letter. On July 24, 2015, FDA received an unsolicited amendment (SE0012212)[2] informing FDA that SE Reports subject of this review and originally owned by RJRT were transferred to ITGB on June 12, 2015. Additionally, FDA received unsolicited amendments (SE0012328 and SE0012329) from ITGB on September 1, 2015, as a follow up to the FDA's June 11, 2015, Notification letter, as well as to inform FDA of the transfer of ownership to ITGB for the SE Reports. On October 9, 2015, FDA issued a letter stating that FDA has changed its records to identify ITG as the manufacturer of Salem brand products (including those subject to this memo) and as the applicant of record. FDA issued an A/I letter on July 25, 2017. On September 20, 2017, the FDA received a response to the A/I letter (SE0014342). FDA issued a Preliminary Finding (PFind) letter on December 19, 2017. On December 21, 2017, FDA received a 30-day extension request (SE0014439) to respond to the December 19, 2017, PFind letter. On January 3, 2018, FDA issued an Extension Granted letter with a new response due date of February 16, 2018. On February 14, 2018, FDA received an amendment (SE0014529) in response to the December 19, 2017, PFind letter. On February 15, 2018, SE0014529 was replaced by another amendment (SE0014532) due to decimal points missing in the previously submitted tables. On February 20, 2018, FDA received an unsolicited amendment (SE0014542) in which ITGB officially states that the February 15, 2018, amendment (SE0014532) replaces the February 14, 2018 amendment (SE0014529) as the response to the PFind letter. On May 30, 2018, an unsolicited amendment (SE0014735) was received as an additional response to the December 19, 2017, PFind letter. However, this amendment was received after all scientific reviews were completed. The technical project lead of this TPL review examined this amendment and determined that this information does not change the overall conclusion of this TPL review.

[2] Related to inactive duplicate amendments SE0012208 and SE0012209

Product Name	SE Report	Amendments
Salem Box	SE0006259	SE0007894 SE0008212 SE0008917 SE0011977 SE0012011 SE0012014 SE0012167 SE0012168 SE0012212[2] SE0012328 SE0014342 SE0014439 SE0014452 SE0014529 SE0014532 SE0014542 SE0014735
Salem Slim 100's Box	SE0006260	SE0007894 SE0008212 SE0008881 SE0012011 SE0012014 SE0012167 SE0012168 SE0012212[2] SE0012329 SE0014342 SE0014439 SE0014452 SE0014529 SE0014532 SE0014542 SE0014735

1.3. SCOPE OF REVIEW

This review captures all regulatory, compliance, and scientific reviews completed for these SE Reports.

2. REGULATORY REVIEW

Regulatory reviews were completed by Marcella White on March 25, 2013.

The reviews conclude that these SE Reports were *not* administratively complete because the following information was not included in the SE Reports:

1. Rationale for SE related to new tobacco product
2. Heating source
3. Unique identification of the predicate products
4. Health information
5. Characteristic comparisons of new and predicate product
6. Standards under Section 907
7. Date of new products commercially marketed
8. Environmental assessment

This information was provided during the scientific review process. Therefore, these SE Reports are administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews to determine whether the applicant established that the predicate tobacco products are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007). The OCE reviews dated July 14, 2015, conclude that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco products are grandfathered and, therefore, are eligible predicate tobacco products.

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 Jeffrey Ammann, on April 4, 2016, and by Stephanie Daniels on December 15, 2017, and April 13, 2018.

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

1. Both of your SE Reports contain several discrepancies for the tobacco blend types for The new and predicate products listed in your September 20, 2017 amendment. The tobacco blend composition and quantities have changed compared to the information you submitted previously. The new and predicate products originally contained (b)(4) [redacted]; however, the new product and predicate/remanufactured products submitted in the September 20, 2017, amendment list only [redacted]. Thus, the new product of SE0006259 contains [redacted]

and [redacted] compared to the predicate product. These increases may affect mainstream smoke and cause the new product to raise different questions of public health. It is unclear which subcomponents of the tobacco types were grouped together and how the quantities were calculated. Without this information, we cannot determine if these differences cause the new products to raise different questions of public health. Provide detailed information on how the [redacted] were simplified and combined and why higher levels of [redacted] in the new products do not raise different questions of public health.

2. Both of your SE Reports state that the new products have higher amounts or different ingredients in the remanufactured predicate products compared to the corresponding new products. Specifically:
   a) For SE0006259, the [redacted] are 186% and 811% higher, respectively, than the remanufactured predicate product. Additionally, [redacted] being 844% higher than the remanufactured predicate product.
   b) For SE0006260, [redacted] in the tobacco, are 55%, 44%, 68%, and 1,240% higher, respectively, than the remanufactured predicate product.
   c) Both of your SE Reports identify ingredients added to the new products which are not present in the corresponding remanufactured predicate products. For SE0006259, [redacted] was added to the tobacco of the new product, in addition, ingredients were added to the cigarette paper, tipping paper adhesive, filter center line adhesive, and tipping paper adhesive. For SE0006260, [redacted] was added along with other ingredients to the cigarette paper, tipping paper adhesive, filter center line adhesive, and tipping paper.

   Such changes are expected to have an impact on smoke chemistry. Sugars are known to increase the mainstream smoke yields of certain carbonyls and hydrocarbons, such as formaldehyde, acrolein, and benzene. A decrease in sugars has been shown to increase NNN, NNK, and 4-aminobiphenyl. In addition, sugars and other flavors are used in tobacco products to mitigate the harshness of cigarette smoke or to enhance the product's appeal. Additionally, phenol smoke yield in SE0006259 was 19% higher under ISO smoking conditions and 27% higher under Cl smoking conditions for the new compared to the remanufactured predicate product. Provide scientific evidence and rationale as to why the differences in the ingredients of the new products does not cause them to raise different questions of public health.

3. Both of your SE Reports contain discrepancies for the number of sample replicates for TNCO data reported in your summary table for the new and remanufactured predicate products. You state the number of sample replicates was 20; however, the test data you provided and the summary tables are based on 23 and 24 sample replicates for the new and remanufactured predicate products, respectively. Provide an explanation for this discrepancy.

4. SE0006259 indicates that there are discrepancies in the ingredients listed for the filter tow in the most recent amendment dated February 15, 2018 for the remanufactured

predicate product. For example, the reported quantity for [redacted] in the remanufactured predicate product is (b) (4) /cigarette in the September 20, 2017 response to the A/I letter and (b) (4) /cigarette in the February 15, 2018 response to the PFind letter. The values reported in the 2017 and 2018 amendments differ by (b) (4) /cigarette. This discrepancy in reported [redacted] levels may cause the new product to raise different questions of public health. Provide an explanation for this discrepancy.

5. Both of your SE Reports include data comparing the quantities of HPHCs in filler in the new and remanufactured predicate products. For SE0006260, the ammonia and NNN levels in the new product are 40% and 14% higher, respectively, than the corresponding remanufactured predicate products. Provide scientific evidence and rationale as to why the difference in ammonia and NNN levels does not cause the new products to raise different questions of public health.

6. Both of your SE Reports include data comparing the quantities of HPHCs in the new and remanufactured predicate products. You report HPHC smoke yields that are higher in the new products compared to the corresponding remanufactured predicate products in both SE Reports. Specifically,
    a) For SE0006259, 27% higher NNK and 24% higher NNN under ISO smoking conditions and 40% higher 4-aminobiphenyl; 64% higher NNK, and 59% higher NNN under CI smoking conditions.
    b) For SE0006260, 30% higher NNK and 35% higher NNN under ISO smoking conditions; 33% higher NNK; and 16% higher NNN under CI smoking conditions.

    Provide an explanation why the higher amounts of these HPHCs do not cause the new products 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 corresponding 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 Aarthi Arab, on March 25, 2016, by Julie Morabito on December 18, 2017, and by Gloria Kulesa on May 10, 2018.

The final engineering review concludes that the new tobacco products have different characteristics related to product engineering compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate the differences do not

[3] This is an error. The correct term is "[redacted]."

cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. Both of your SE Reports contain side-by-side comparisons of all of the necessary design parameter target specifications and upper and lower range limits for the predicate products and corresponding remanufactured predicate products for both SE Reports. However, for the new and predicate tobacco products for both SE Reports, your response to the December 2017 Preliminary Finding letter includes inconsistencies in the target specifications of several design parameters from those provided in your previous submissions. You state that the target specifications have been updated since the previous submission and indicate that differences in the values are due to reporting errors that you have noted or to the rounding to different significant figures between submissions. However, for the new and predicate tobacco products for both SE Reports, the differences in the target specifications among your submissions is too great to be due to differences in significant figures. Furthermore, the parameter values have changed across multiple submissions, which limits the possibility of the error being due to reporting mistakes. You may not retroactively change the new and predicate tobacco products that are subject of the original SE Reports. If you choose to use remanufactured predicate products to extrapolate test data to the corresponding predicate products, then the predicate products and corresponding remanufactured predicate products must be fully characterized to determine whether the remanufactured predicate product test data can be extrapolated to the predicate products.

   Accordingly, the actual target specifications and range limits of these design parameters are unclear, which precludes an evaluation of whether the remanufactured predicate products are equivalent to the corresponding predicate products to permit the use of test data from the remanufactured predicate products in place of test data from the predicate products themselves. As such, you have not adequately justified why differences to the design parameters do not cause the new products to raise different questions of public health.

   Therefore, clarify the inconsistencies in the design parameter target specifications and upper and lower range limits provided in the response to the December 2017 Preliminary Finding letter compared to those provided in previous submissions, as indicated below:

   Target specification and upper and lower range limits

   a. Cigarette draw resistance (SE0006260, new product)
   b. Tobacco filler mass (both SE Reports, new products)
   c. Tobacco rod density (both SE Reports, new products)
   d. Cigarette paper band porosity (SE0006260, predicate product)
   e. Filter density (SE0006260, new and predicate products)

   Target specification

   a. Cigarette paper base paper basis weight (SE0006260, predicate product)
   b. Filter total denier (both SE Reports, new and predicate products)

c. Filter denier per filament (both SE Reports, new and predicate products)
d. Filter density (SE0006259, new and predicate products)

Upper and lower range limits

a. Tobacco rod density (both SE Reports, predicate products)
b. Cigarette paper base paper basis weight (SE0006259, new product)
c. Cigarette paper base paper porosity (SE0006259, new product; SE0006260, new and predicate products)
d. Cigarette paper band width (SE0006259, new product)
e. Cigarette paper band space (SE0006259, new product)
f. Filter total denier (SE0006260, new and predicate products)
g. Filter ventilation (SE0006259, new and predicate products; SE0006260, new product)

Additionally, differences in design parameters between the new and predicate tobacco products for both SE Reports may cause the new products to raise different questions of public health. Therefore, provide scientific justification for why the differences to cigarette draw resistance, cigarette paper base paper basis weight, cigarette paper base paper porosity, cigarette paper band width, cigarette paper band space, filter total denier, and filter density between the new and predicate tobacco products for SE0006259 do not cause the new product to raise different questions of public health. Further, provide scientific justification for why the differences to cigarette draw resistance and cigarette paper band space between the new and predicate tobacco products for SE0006260 do not cause the new product to raise different questions of public health.

For each of the above parameters, provide the necessary data on a per unit of measurement of product basis (e.g., cigarette paper band width should be reported in mm per cigarette). If a design parameter is not applicable state as such.

2. Both of your SE Reports provide the target specifications and upper and lower range limits for cigarette paper band diffusivity, but not for cigarette paper band porosity for the new products, for both SE Reports. Additionally, you provide the target specifications and upper and lower range limits for cigarette paper band porosity, but not for cigarette paper band diffusivity for the predicate products for both SE Reports. Band porosity and band diffusivity are not identical parameters and are not interchangeably used. Diffusivity mimics air flow during smoldering and is mainly used for predicting cigarette burn rates. Band porosity measures air permeability, allowing for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. The measurement of cigarette paper band porosity thereby relates directly to TNCO exposure. Furthermore, since band porosity allows for the overall assessment of the change in air flow, band porosity information is needed to adequately characterize the new products. In addition, you do not provide a correlation between diffusivity and porosity to allow for a scientific comparison and evaluation of how the two design parameters can be extrapolated to one another. You provide a study performed by your cigarette paper material supplier to demonstrate that you have not determined a means by which to correlate cigarette paper band

porosity to cigarette paper band diffusivity. However, without the target specifications and upper and lower range limits for either (a) cigarette paper band porosity for the new products or (b) cigarette paper band diffusivity for the predicate products, a comparison cannot be made between the new and predicate tobacco products. Differences to cigarette paper band porosity may influence the burn characteristics of the cigarette, as well as air flow through the tobacco column, which may cause the new products to raise different questions of public health. Therefore, for both SE Reports, provide either the target specifications and upper and lower range limits for cigarette paper band porosity for the new products or the target specifications and upper and lower range limits for cigarette paper band diffusivity for the predicate products. If a difference in cigarette paper band porosity exists between the new and corresponding predicate tobacco products, provide a rationale for each difference in the target specification with evidence and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

Additionally, for both SE Reports, the certificates of analysis (COAs) for cigarette paper band porosity do not include the target specification and upper and lower range limits for cigarette paper band porosity for the new products. COAs used to confirm whether design parameters have been met must include the target specification; quantitative acceptance criteria; parameter units; test data average value; and the minimum and maximum values of the test data. The certificate of analysis must be a complete, unaltered certificate of analysis from the material supplier. Without the target specifications and upper and lower range limits, the COAs cannot be used to confirm whether the specifications for cigarette paper band porosity have been met for the new products, for both SE Reports. Additionally, if you choose to provide a COA to confirm whether the specification for cigarette paper band porosity has been met for the predicate product for SE0006260, the COA should contain the target specification and lower range limit for cigarette paper band porosity. As such, provide complete COAs for cigarette paper band porosity for the new products for both SE Reports and the predicate product for SE0006260.

3. Both of your SE Reports include specifications for tobacco filler mass and filter density for the predicate products, but do not include all of the necessary test data confirming that the specifications are met. Test data are measured values of design parameters and include test protocols, quantitative acceptance criteria, data sets, and a summary of the results. You provide design parameter test data from remanufactured predicate products to be extrapolated to the predicate products, but the remanufactured predicate product test data cannot be extrapolated to the predicate products due to inconsistencies in the values of design parameters among your submissions. Therefore, provide the test data (i.e. measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results or unaltered material supplier COA (including the design parameter target specification, quantitative acceptance criteria, parameter units, test data average value, and the minimum and maximum values of the test data) for tobacco filler mass and filter density for the predicate products, for both SE Reports. For each of the above parameters, provide the necessary data on a per unit of measurement of product basis (e.g., tobacco filler mass should be reported in mg per cigarette).

Additionally, for the design parameters listed above that were tested according to national or international standards, identify the standards and state what deviations, if any, from the standards occurred.

4. SE0006259 contains updated target specifications for filter total denier that indicate that the filter total denier of the new product is higher than the filter total denier of the predicate product in your recent submission. Changes to the filter filaments influence filtration efficiency, which may cause the new product to raise different questions of public health. Therefore, provide scientific justification for why the difference in filter total denier between the new and predicate tobacco product for SE0006259 does not cause the new product to raise different questions of public health.

5. SE0006259 indicates that the puff count of the new product is higher than the puff count of the predicate product in your response to the December 2017 Preliminary Finding letter. Additionally, for the new product for SE0006259, the puff count values you provided in response to the December 2017 Preliminary Finding letter are inconsistent with the puff count values you provided in previous submissions. An increase in puff count may increase smoke constituent yields, causing the new product to raise different questions of public health. Therefore, for SE0006259, clarify the inconsistency in the puff count values among submissions for the new product. Additionally, provide scientific rationale for why the increase in puff count does not cause the new product for SE0006259 to raise different questions of public health.

6. SE0006260 indicates that the puff count test data for the predicate product is based on the FTC smoking regime, whereas the puff count test data for the new product is based on the ISO smoking regime in your response to the December 2017 Preliminary Finding letter. To permit a comparison between the two smoking machine methods, the FTC-based puff count was reduced by 10%. With this adjustment, the puff count of the new product is higher than the puff count of the predicate product. An increase in puff count may increase smoke constituent yields. As such, provide scientific justification for why the increase in puff count for SE0006260 does not cause the new products to raise different questions of public health.

7. SE0006259 indicates that that the decreases in cigarette paper band space and filter density are offset by an increase in filter ventilation between the new and predicate tobacco products. While an increase in filter ventilation may offset decreases in cigarette paper band space and filter density, you have not provided scientific justification for how the magnitude of difference to filter ventilation offsets the decreases in cigarette paper band space and filter density such that the differences in cigarette paper band space and filter density are not likely to cause the new product to raise different questions of public health. You also refer to the smoke constituent test data for the new product and the remanufactured predicate product to justify why these design parameter differences do not cause the new product to raise different questions of public health. However, inconsistencies in the target specifications and range limits of several design parameters for the new and predicate tobacco products prevents the evaluation of the suitability of the remanufactured predicate product test data. Therefore, provide scientific justification for why the differences in cigarette paper

band space and filter density for SE0006259 do 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 corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from an engineering perspective.

4.3. TOXICOLOGY

Toxicology reviews were completed by Sang Park, on July 11, 2017, December 11, 2017, and May 17, 2018.

The final toxicology review concludes that the new tobacco products have different characteristics related to product toxicity compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies that have *not* been adequately resolved:

1. Both of your SE Reports indicate the following ingredients are added or increased in the tobacco blends of the new products compared to the corresponding predicate products:

    a. (b) (4) : SE0006260
    b. (b) (4) : SE0006259 & SE0006260

    Both of these ingredients have the potential to change the smoke profile by being directly transferred to the cigarette smoke without structural changes through distillation/volatilization during smoking. However, you did not provide sufficient evidence to support that the ingredient changes do not cause the new products to raise different questions of public health. Provide scientific evidence and rationale explaining why the addition or increase in quantity of the aforementioned ingredients does not cause the new products to raise different questions of public health.

    If you choose to reference research studies, explain how each reference supports the specific comparison between the new and predicate products. Provide a rationale explaining how data generated using the experimental cigarettes evaluated in the referenced studies can be extrapolated to the new and predicate products, taking into account cigarette composition and smoke dilution methods. Explain how data extrapolated from these references supports the conclusion that the different characteristics in your new products as compared to the corresponding predicate products do not cause the new products to raise different questions of public health. If referenced studies assess non-inhalation toxicity of an ingredient (e.g., as in oral toxicity studies), explain how data generated from non-inhalation route of exposure can be extrapolated to the evaluation of potential inhalation toxicity.

2. SE0006259 indicates the following ingredients are added or increased in the new product compared to the predicate product:

a. (b) (4) [redacted]
b.
c.
d.
e.
f.

Because all of these ingredients are expected to be combusted, they have the potential to change the smoke profile by undergoing combustion/pyrolysis, for instance increasing phenol or cresol. The HPHC data that you provided shows that phenol and cresols are significantly increased in the mainstream smoke of the new product compared to the corresponding remanufactured predicate product under HCI smoking regime. However, you did not provide sufficient evidence to support the ingredient changes do not cause the new product to raise different questions of public health. Provide scientific evidence and rationale explaining why the addition or increase in quantity of the aforementioned ingredients, and their respective pyrolysis byproducts, do not cause the new product to raise different questions of public health.

3. Both of your SE Reports include a voluntarily submitted quantitative risk assessment (QRA) and probabilistic risk assessment (PRA) to support that the changes in tobaccos and tobacco ingredients, and increases in multiple HPHC levels do not cause the new products to raise different questions of public health. The QRA/PRA submitted with your SE Reports, did not provide key information needed to evaluate the HPHC changes between the new and corresponding predicate products.

   While a QRA/PRA is not required for a substantial equivalence evaluation, such analyses can inform the review process, if adequately described and supported. For FDA to review any risk assessment that is voluntarily included in an application, provide a detailed account of the QRA and PRA preferably completed in line with recommendations from the National Academy of Sciences (NRC, 2009) as much as possible. In addition, provide all data and a detailed description of the results and analysis of the QRA and PRA to demonstrate that user exposure to the new products will not lead to increased toxicity or overall health risk compared to the corresponding predicate products.

   The data, results, and analysis of the QRAs and PRAs provided are either unclear or lack sufficient details:

   a. Provide additional information on how the cumulative HQ and cumulative ILCR values were calculated, including 1) which HPHCs were included in the calculation of the cumulative values, 2) justification for the smoke HPHCs included, 3) detailed description of each calculation, 4) a scientific rationale for not assessing cumulative hazard or risk in the QRAs and 5) how to interpret the results of the cumulative ILCR and HQ (HI) based on distribution means resulting from the PRAs. If there is any HPHC that is significantly different in an analytically meaningful way in the new product compared to the corresponding remanufactured predicate product, but was not included in the calculation of

cumulative HQ/cumulative ILCR, provide an explanation as to how the omission of any HPHC can impact the results of the QRA or PRA.

b. You provided the HQ estimates of phenol, *m-p*-cresol and *o*-cresol for the new and remanufactured predicate products in SE0006259 (*Table 16d.3-1: HQ Estimates for the Subject vs. Reman Predicate Under ISO Conditions & Table 16d.3-2: HQ Estimates for the Subject vs. Reman Predicate Under HCI Conditions, p1422 & 1423*, SE0014532). Even though these HPHCs are increased in the mainstream smoke of the new product compared to the remanufactured predicate product, the HQ values of the new product are reported to be 19 – 151-fold smaller than those of the remanufactured predicate product. Clarify why the HQ estimates for phenol, o-cresol, and m-p-cresol are smaller for the new product than for the predicate product, despite their increased smoke yields in the new product compared to the predicate product in SE0006259.
c. Provide a detailed explanation of any route-to-route extrapolations, including input data, assumptions, equations and outputs.
d. Provide detailed selection criteria for the selection of reference values and scientific evidence for deviating from established reference values. Include additional evidence or rationale for selected reference values, given the availability of multiple reference values for a specific constituent. Any rationale should include scientific evidence for deviating in methodology from the National Research Council and the Guidelines for Carcinogen Risk Assessment.
e. Provide evidence that the reference values used in the calculation of the HQ or ILCR, and used in both the QRA and PRA, are appropriate for the toxicological endpoints associated with the use of the new and predicate products.
f. In the 'Problem Formulation' section, you state that "*the risk assessment (i.e., QRA) presented herein does not concern absolute risk or hazard but rather the comparative risk or hazard between the two products (i.e., Subject and Reman Predicate/Predicate).*" However, you provided data and a discussion relating to the absolute risk or hazard (e.g., the total cancer risk or margin-of-exposure). Provide clear description of how you intend to characterize and interpret the QRA and PRA results.
g. Provide specific evidence or rationale for the inclusion of body weight and daily inhalation rate in your estimation of exposure concentrations regarding the smoker exposure scenario.
h. Provide clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime is appropriate for the specific products and user populations.
i. Provide all raw data, equations, assumptions, parameters, outputs, and references used in the QRA and PRA, including the HPHC data, methods used to determine statistical variability and any other pertinent data used in these calculations.
j. Provide a complete description of the PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. For example, although the assumed minimum, maximum and "likeliest" values for the distributions are provided, no justifications for the use of Beta PERT distributions (used for Cigarettes per Day (CpD), Exposure Duration (ED), Averaging Time (AT)) or Gamma distribution (used for Daily Inhalation Rate (DIR)) are given. Provide scientific evidence that the parameter ranges and

means are specific to the new and predicate products and the expected user populations. Consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions.

k. Provide scientific evidence and rationale demonstrating that the distributions for each parameter and the ranges are appropriate given the characteristics of the new and predicate products and the anticipated user population of both products. Any rationale or scientific evidence needs to also include further discussion as to the quality and appropriateness of the inputs as well as the PRA expectations that the resulting parameter estimations accurately reflect the real product or user specific values.

l. Provide evidence that the daily inhalation parameter used in the reference you cited, Marano et al, 2012, 193.99 L/kg-d, is appropriate for tobacco product-specific exposures as well as the population expected to use the new and predicate products.

m. You provided PRA results to characterize uncertainty and variation associated with exposure-related parameters. However, the PRA does not include sufficient and clear description on several aspects of computational methodology, input parameters, and interpretation of the assessment results. Importantly, the PRA does not address uncertainties inherent to other critical elements in the QRA. In discussing uncertainty and variability, provide an assessment of the PRA's ability to discern a statistical difference in risk between tobacco products. Provide sufficient characterization of uncertainties and variation of all other critical elements in risk assessment processes, such as:

    1) Uncertainty in the use of addition for estimating total hazard or risk from components of a mixture in which other interactions may occur or the available information indicates combinations other than additivity regarding dose effects and adverse health outcomes.
    2) Uncertainty of representing the total adverse health risks of the new and predicate cigarette products with a small number of constituents selected for the QRA/PRA.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a toxicology perspective.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order finding a tobacco product Not Substantially Equivalent (NSE) under section 910(a) of the FD&C Act is categorically excluded and, therefore, normally does not require the preparation of an environmental assessment (EA) or 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.

The applicant has failed to demonstrate that the following differences in characteristics do not cause the new tobacco products to raise different questions of public health. The applicant submitted tobacco blend, structural materials, and ingredients for the new, predicate, and remanufactured predicate products. However, the applicant has failed to provide adequate information of the tobacco blends and ingredients such as (b) (4) [redacted] to demonstrate these differences between the new and predicate tobacco products do not cause the new products to raise different question of public health. The applicant also remanufactured the predicate products and included information for these products. Based on the information provided by the applicant for the predicate and remanufactured predicate products for both SE Reports, the tobacco blends are identical with minor differences in the structural materials between the predicate and remanufactured predicate products. For both SE Reports, NNK and NNN yields are significantly higher from the new products than the corresponding predicate products under ISO and CI smoking regimens. The applicant provided a quantitative risk assessment and a probabilistic risk assessment to demonstrate that the differences in these and other HPHCs do not cause the new products to raise different questions of public health. Nonetheless, the provided assessments lacked information necessary for toxicology to determine that these HPHC differences do not cause the new products to raise different questions of public health.

The applicant also provided design parameter specifications; however, there are inconsistencies in design parameter target specifications and upper and lower range limits for the new and corresponding predicate tobacco products across the applicant's submissions. Engineering was unable to extrapolate the remanufactured predicate product to the predicate product as the applicant did not demonstrate that the same specifications, including upper and lower limits, were met between the remanufactured predicate products and that of the predicate products. The applicant did not provide adequate scientific justification for why differences (calculated based on the latest information submitted by the applicant) to several design parameters do not cause the new products to raise different questions of public health. For SE0006259, differences to cigarette draw resistance, cigarette paper base paper basis weight, cigarette paper base paper porosity, cigarette paper band width, cigarette paper band space, filter total denier, and filter density may influence air flow dynamics, burn characteristics, and filtration efficiency. These differences in design parameters may lead to increased smoke constituent yields, causing the new product to raise different questions of public health. Additionally, for SE0006260, differences to cigarette draw resistance and cigarette paper band space may increase smoke constituent yields by altering the air flow dynamics and burn characteristics within the tobacco column, which may cause the new product to raise different questions of public health. Furthermore, the applicant does not provide the complete test data for all of the necessary design parameters sufficient to confirm whether design parameter specifications have been met. Accordingly, the applicant has not demonstrated whether all of the design parameter specifications have been met. Therefore, the applicant has failed to provide sufficient information to for FDA to determine that the new products do not raise different questions of public health.

The predicate tobacco products meet statutory requirements because it was determined that they are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007).

The chemistry, engineering, and toxicology reviews conclude that the new tobacco products have different characteristics compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new

tobacco products to raise different questions of public health. I concur with these reviews and recommend that NSE order letters be issued.

Because the proposed action is issuing NSE orders, it is a class of action that is categorically excluded under 21 CFR 25.35(b). FDA has considered whether there are extraordinary circumstance 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.

NSE order letters should be issued for the new tobacco products in SE0006259 and SE0006260, as identified on the cover page of this review.

6.1. DEFICIENCIES FOR SE006259

The NSE order letter for SE0006259 should cite the following deficiencies:

1. Your SE Report contains several discrepancies in the tobacco blend types for the new and predicate products listed in your September 20, 2017 amendment. The tobacco blend composition and quantities have changed compared to the information you submitted previously. The new and predicate products originally contained (b) (4) ; however, the new product and predicate/remanufactured products submitted in the September 20, 2017, amendment list only : which indicates increase in thosetobacco types. Based on the information provided in your SE Report, it is unclear which subcomponents of the tobacco types were grouped together and how the quantities were calculated. Without this information, we cannot determine if these differences cause the new products to raise different questions of public health. You needed to provide clear and detailed information on how the were simplified and combined and why higher levels of the different tobacco types such as do not cause the new product to raise different questions of public health.

2. Your SE Report states that the new product has higher amounts or different ingredients in the new product compared to the remanufactured predicate product which is used in lieu of the predicate product. Specifically, the and are 186% and 811% higher, respectively, than the remanufactured predicate product. Furthermore, is 844% higher than the remanufactured predicate product. Additionally, was added to the tobacco of the new product, in addition, ingredients were added to the cigarette paper, tipping paper adhesive, filter center line adhesive, and tipping paper adhesive.

   Such changes are expected to have an impact on smoke chemistry. Sugars, such as those found in (b) (4) , are known to increase the mainstream smoke yields of certain carbonyls and hydrocarbons, such as formaldehyde, acrolein, and benzene. A decrease in sugars has been shown to increase NNN, NNK, and 4-aminobiphenyl. In addition, sugars and other flavors, such as and , are used in tobacco products to mitigate the harshness of cigarette smoke or to enhance the product's appeal. You needed to provide scientific evidence and rationale

as to why the differences in the ingredients between the new and predicate products do not cause the new product to raise different questions of public health.

3. Your SE Report contains discrepancies in the number of sample replicates for TNCO data reported in your summary table for the new and remanufactured predicate products. You state the number of sample replicates was 20; however, the test data you provided and the summary tables are based on 23 and 24 sample replicates for the new and remanufactured predicate products, respectively. You needed to clarify this discrepancy as FDA is unable which number of replaicates is accurate and how many measuremenrts were conducted in order to analyze the TNCO yields as without accurate information FDA is unable to determine if this information causes the new product to raise different questions of public health.

4. Your SE Report indicates that there are discrepancies between amendments in the ingredients listed for the filter tow of the remanufactured predicate product. For example, the reported quantity for (b) (4) in the remanufactured predicate product is (b) (4) /cigarette in the September 20, 2017 amendment and (b) (4) /cigarette in the February 15, 2018 amendment. The values reported in the 2017 and 2018 amendments differ by (b) (4) cigarette. You needed to clarify this discrepancy as FDA is unable to determine which value is correct in order to evlaute the ingredient changes between the new and predicate tobacco product as without accurate information FDA is unable to determine if this changes causes the new product to raise different questions of public health.

5. Your SE Report includes inconsistencies in the target specifications of several design parameters when comparing your December 2017 amendment to your earlier amendments. You state that the target specifications have been updated since the previous amendments and indicate that differences in the values are due to reporting errors that you have noted or to the rounding to different significant figures between amendments. Furthermore, the parameter values have changed across multiple amendments, which indicates that the error is likely to be attributable to reporting mistakes. If the remanufactured predicate product test data cannot be extrapolated to the predicate product, FDA is unable to determine whether the new product has different design parameters than the predicate product.

   Therefore, you needed to clarify the inconsistencies in the design parameter target specifications and upper and lower range limits provided in the December 2017 amendment compared to those provided in the original SE Report and earlier amendments, as indicated below:

   a. Target specification and upper and lower range limits
      i. Tobacco filler mass (new product)
      ii. Tobacco rod density (new product)
   b. Target specification
      i. Filter total denier (new and predicate products)
      ii. Filter denier per filament (new and predicate products)
      iii. Filter density (new and predicate products)

c. Upper and lower range limits
    i. Tobacco rod density (predicate product)
    ii. Cigarette paper base paper basis weight (new product)
    iii. Cigarette paper base paper porosity (new product)
    iv. Cigarette paper band width (new product)
    v. Cigarette paper band space (new product)
    vi. Filter ventilation (new and predicate products)

Additionally, differences in design parameters between the new and predicate tobacco products may cause the new product to raise different questions of public health. Therefore, you needed to provide scientific justification for why the differences in *all* of the following design parameters do not cause the new product to raise different questions of public health:

d. Cigarette draw resistance
e. Cigarette paper base paper basis weight
f. Cigarette paper base paper porosity
g. Cigarette paper band width
h. Cigarette paper band space
i. Filter total denier
j. Filter density

6. Your SE Report provides the target specifications and upper and lower range limits for cigarette paper band diffusivity, but not for cigarette paper band porosity for the new product. Additionally, you provide the target specifications and upper and lower range limits for cigarette paper band porosity, but not for cigarette paper band diffusivity for the predicate product. Band porosity and band diffusivity are not identical parameters and are not interchangeably used. Diffusivity mimics air flow during smoldering and is mainly used for predicting cigarette burn rates. Band porosity measures air permeability, allowing for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. The measurement of cigarette paper band porosity thereby relates directly to TNCO exposure. Furthermore, since band porosity allows for the overall assessment of the change in air flow, band porosity information is needed to adequately characterize the new products. In addition, you do not provide a correlation between diffusivity and porosity to allow for a scientific comparison and evaluation of how the two design parameters can be extrapolated to one another. You did provide a study performed by your cigarette paper material supplier, however this study does not demonstrate a means to correlate cigarette paper band porosity to cigarette paper band diffusivity. However, without the target specifications and upper and lower range limits for either (a) cigarette paper band porosity for the new product or (b) cigarette paper band diffusivity for the predicate product, a comparison cannot be made between the new and predicate tobacco products. Differences to cigarette paper band porosity may influence the burn characteristics of the cigarette, as well as air flow through the tobacco column, which may cause the new products to raise different questions of public health. Therefore, you needed to provide either the target specifications and upper and lower range limits for cigarette paper band porosity for the new product or the target specifications and upper and lower range limits for cigarette paper band diffusivity for the predicate

product. If a difference in cigarette paper band porosity exists between the new and predicate tobacco products, you needed to provide a rationale for each difference in the target specification with evidence and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

Additionally, the certificate of analysis (COA) for cigarette paper band porosity does not include the target specification and upper and lower range limits for cigarette paper band porosity for the new product. COAs are used to confirm whether design parameters have been met must include the target specification; quantitative acceptance criteria; parameter units; test data average value; and the minimum and maximum values of the test data. The COA should be a complete, unaltered certificate of analysis from the material supplier. Without the target specifications and upper and lower range limits, the COA cannot be used to confirm whether the specifications for cigarette paper band porosity have been met for the new product. You needed to provide complete COAs for cigarette paper band porosity for the new product.

7. Your SE Report includes specifications for tobacco filler mass and filter density for the predicate product, but does not include test data sufficient to confirm that the specifications are met. Test data are measured values of design parameters and include test protocols, quantitative acceptance criteria, data sets, and a summary of the results. You provide design parameter test data from the remanufactured predicate product to be extrapolated to the predicate product, but the remanufactured predicate product test data cannot be extrapolated to the predicate products due to inconsistencies in the values of design parameters among your amendments. Therefore, you needed to provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results or unaltered material supplier COA (including the design parameter target specification, quantitative acceptance criteria, parameter units, test data average value, and the minimum and maximum values of the test data) for the tobacco filler mass and filter density for the predicate product. For each of the above parameters, you also needed to provide the necessary data on a per unit of measurement of product basis (e.g., tobacco filler mass should be reported in mg per cigarette). FDA is unable to make a comparison between the new product and the predicate product because the surrogate predicate product cannot be extrapolated to the predicate product for the provided engineering parameters.

8. Your SE Report contains updated target specifications for filter total denier that indicate that the filter total denier of the new product is higher than the filter total denier of the predicate product in your December 2017 amendment. Changes to the filter filaments influence filtration efficiency, which may cause the new product to raise different questions of public health. Therefore, you needed to provide scientific justification for why the difference in the filter total denier between the new and predicate tobacco products does not cause the new product to raise different questions of public health.

9. Your SE Report indicates that the puff count of the new product is higher than the puff count of the predicate product in your December 2017 amendment. Additionally, for the new product, the puff count test data you provided in response to the December 2017 amendment are inconsistent with the puff count test data you provided in earlier

amendments. An increase in puff count may increase smoke constituent yields, causing the new product to raise different questions of public health. Therefore, you needed to clarify the inconsistency in the puff count test data among the amendments for the new product. Additionally, you needed to provide a scientific rationale for why the increase in puff count does not cause the new product to raise different questions of public health.

10. Your SE Report indicates that that the decreases in cigarette paper band space and filter density are offset by an increase in filter ventilation between the new and predicate tobacco products. While an increase in filter ventilation may offset decreases in cigarette paper band space and filter density, you have not provided scientific justification for how the magnitude of difference to the filter ventilation offsets the decreases in cigarette paper band space and filter density such that the differences in cigarette paper band space and filter density do not cause the new product to raise different questions of public health. You also refer to the smoke constituent test data for the new product and the remanufactured predicate product to justify why these design parameter differences do not cause the new product to raise different questions of public health. However, inconsistencies in the target specifications and range limits of several design parameters for the new and predicate tobacco products prevents the evaluation of the suitability of the remanufactured predicate product test data. Therefore, you needed to provide scientific justification for why the differences in cigarette paper band space and filter density do not cause the new product to raise different questions of public health.

11. Your SE Report indicates that (b) (4) is increased in the new product compared to the predicate product. This ingredient has the potential to change the smoke profile by being directly transferred to the cigarette smoke without structural changes through distillation/volatilization during smoking. However, you did not provide sufficient evidence to support that the ingredient increase does not cause the new product to raise different questions of public health. You needed to provide scientific evidence and rationale explaining why the increase in quantity of this ingredient does not cause the new product to raise different questions of public health. One way you may have satisfied this concern is by providing a rationale explaining how data generated using the experimental cigarettes evaluated in referenced scientific studies can be extrapolated to the new and predicate products, taking into account cigarette composition and smoke dilution methods. If you elected to do so, you would have needed to explain how data extrapolated from such references supports the conclusion that the different characteristics in your new product as compared to the predicate product does not cause the new product to raise different questions of public health.

12. Your SE Report indicates the following ingredients are added or increased in the new product compared to the predicate product:

    a. (b) (4)
    b.
    c.
    d.
    e.

f. (b) (4) [redacted]

Because all of these ingredients are expected to be combusted, they have the potential to change the smoke profile by undergoing combustion/pyrolysis, for example increasing phenol or cresol. The HPHC data that you provided shows that phenol and cresols are significantly increased in the mainstream smoke of the new product compared to the corresponding remanufactured predicate product under CI smoking conditions. However, you did not provide sufficient evidence to support a claim that the ingredient changes do not cause the new product to raise different questions of public health. You needed to provide scientific evidence and rationale explaining why the addition or increase in quantity of these ingredients, and the respective pyrolysis byproducts, do not cause the new product to raise different questions of public health.

13. Your SE Report includes a voluntarily submitted quantitative risk assessment (QRA) and probabilistic risk assessment (PRA) to support the position that the changes in tobaccos and tobacco ingredients, and increases in multiple HPHC levels do not cause the new product to raise different questions of public health. Specifically, the new product demonstrates a 27% increased NNK and a 24% increased NNN yield under ISO smoking conditions and a 40% increased 4-aminobiphenyl; a 64% increased NNK, and a 59% increased NNN yield under Cl smoking conditions. The submitted QRA/PRA did not provide key information needed to evaluate the HPHC changes between the new and predicate products.

While a QRA/PRA is not required for a substantial equivalence evaluation, such analyses can inform the review process, if adequately described and supported. For FDA to review any risk assessment that is voluntarily included in an application, it is suggested that a detailed account of the QRA and PRA completed be in line with recommendations from the National Academy of Sciences (NRC, 2009). In addition, providing all data and a detailed description of the results and analysis of the QRA and PRA to demonstrate that user exposure to the new products will not lead to increased toxicity or overall health risk compared to the predicate product is recommended.

The data, results, and analysis of the QRAs and PRAs provided are either unclear or lack sufficient details to enable FDA to evaluate whether the changes in tobaccos and tobacco ingredients and increases in multiple HPHCs do not cause the product to raise different questions of public health. Thus, to the extent you provided a QRA/PRA for the purpose of demonstrating that such differences do not cause the new product to raise different questions of public health, you needed to address the following issues and supply additional information:

a. Additional information on how the cumulative HQ and cumulative ILCR values were calculated, including 1) which HPHCs were included in the calculation of the cumulative values, 2) justification for the smoke HPHCs included, 3) detailed description of each calculation, 4) a scientific rationale for not assessing cumulative hazard or risk in the QRAs and 5) how to interpret the results of the cumulative ILCR and HQ (HI) based on distribution means resulting from the PRAs. If there is any HPHC that is significantly different in an analytically meaningful way in the new product compared to the remanufactured predicate

product, but was not included in the calculation of cumulative HQ/cumulative ILCR, an explanation as to how the omission of any HPHC can impact the results of the QRA or PRA is needed.

b. A detailed explanation of any route-to-route extrapolations, including input data, assumptions, equations and outputs.
c. A detailed selection criteria for the selection of reference values and scientific evidence for deviating from established reference values. Include additional evidence or rationale for selected reference values, given the availability of multiple reference values for a specific constituent. Any rationale should include scientific evidence for deviating in methodology from the National Research Council and the Guidelines for Carcinogen Risk Assessment.
d. Evidence that the reference values used in the calculation of the HQ or ILCR, and used in both the QRA and PRA, are appropriate for the toxicological endpoints associated with the use of the new and predicate products.
e. A clear description of how you intend to characterize and interpret the QRA and PRA results. In the 'Problem Formulation' section, you state that "*the risk assessment (i.e., QRA) presented herein does not concern absolute risk or hazard but rather the comparative risk or hazard between the two products (i.e., Subject and Reman Predicate/Predicate).*" However, you provided data and a discussion relating to the absolute risk or hazard (e.g., the total cancer risk or margin-of-exposure).
f. Specific evidence or rationale for the inclusion of body weight and daily inhalation rate in your estimation of exposure concentrations regarding the smoker exposure scenario.
g. Clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime is appropriate for the specific products and user populations.
h. All raw data, equations, assumptions, parameters, outputs, and references used in the QRA and PRA, including the HPHC data, methods used to determine statistical variability and any other pertinent data used in these calculations.
i. A complete description of the PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. For example, although the assumed minimum, maximum and "likeliest" values for the distributions are provided, no justifications for the use of Beta PERT distributions (used for Cigarettes per Day (CpD), Exposure Duration (ED), Averaging Time (AT)) or Gamma distribution (used for Daily Inhalation Rate (DIR)) are given. Provide scientific evidence that the parameter ranges and means are specific to the new and predicate products and the expected user populations. Consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions.
j. Scientific evidence and rationale demonstrating that the distributions for each parameter and the ranges are appropriate given the characteristics of the new and predicate products and the anticipated user population of both products. Any rationale or scientific evidence needs to also include further discussion as to the quality and appropriateness of the inputs as well as the PRA expectations

that the resulting parameter estimations accurately reflect the real product or user specific values.

k. Evidence that the daily inhalation parameter used in the reference you cited, Marano et al, 2012, 193.99 L/kg-d, is appropriate for tobacco product-specific exposures as well as the population expected to use the new and predicate products.

l. Sufficient and clear description on several aspects of computational methodology, input parameters, and interpretation of the assessment results. Importantly, the PRA does not address uncertainties inherent to other critical elements in the QRA. In discussing uncertainty and variability, you needed to provide an assessment of the PRA's ability to discern a statistical difference in risk between tobacco products. You needed to provide sufficient characterization of uncertainties and variation of all other critical elements in risk assessment processes, such as:

   i. Uncertainty in the use of addition for estimating total hazard or risk from components of a mixture in which other interactions may occur or the available information indicates combinations other than additivity regarding dose effects and adverse health outcomes.

   ii. Uncertainty of representing the total adverse health risks of the new and predicate cigarette products with a small number of constituents selected for the QRA/PRA.

6.2. DEFICIENCIES FOR SE006260

The NSE order letter for SE0006260 should cite the following deficiencies:

1. Your SE Report contains several discrepancies in the tobacco blend types for the new and predicate products listed in your September 20, 2017 amendment. The tobacco blend composition and quantities have changed compared to the information you submitted previously. The new and predicate products originally contained [redacted]; however, the new product and predicate/remanufactured products submitted in the September 20, 2017, amendment list only [redacted]: [redacted] which indicate increase in those tobacco types. Based on the information provided in your SE Report, it is unclear which subcomponents of the tobacco types were grouped together and how the quantities were calculated. Without this information, we cannot determine if these differences cause the new products to raise different questions of public health. You needed to provide clear and detailed information on how the [redacted] were simplified and combined and why higher levels of the different tobacco types such as [redacted] do not cause the new product to raise different questions of public health.

2. Your SE Report states that the new product has higher amounts or different ingredients in the new product compared to the remanufactured predicate product which is used in lieu of the predicate product. Specifically, [redacted] in the tobacco, are 55%, 44%, 68%, and 1,240% higher, respectively, than the remanufactured predicate product. Additionally, [redacted] was added along with other ingredients to the cigarette paper, tipping paper adhesive, filter center line adhesive, and tipping paper.

Such changes are expected to have an impact on smoke chemistry. Sugars, such as those found in [redacted], are known to increase the mainstream smoke yields of certain carbonyls and hydrocarbons, such as formaldehyde, acrolein, and benzene. A decrease in sugars has been shown to increase NNN, NNK, and 4-aminobiphenyl. In addition, sugars and other flavors, such as [redacted], are used in tobacco products to mitigate the harshness of cigarette smoke or to enhance the product's appeal. You needed to provide scientific evidence and rationale as to why the differences in the ingredients between the new and predicate products does not cause the new product to raise different questions of public health.

3. Your SE Report contains discrepancies in the number of sample replicates for TNCO data reported in your summary table for the new and remanufactured predicate products. You state the number of sample replicates was 20; however, the test data you provided and the summary tables are based on 23 and 24 sample replicates for the new and remanufactured predicate products, respectively. You needed to clarify this discrepancy as FDA is unable which number of replaicates is accurate and how many measuremenrts were conducted in order to analyze the TNCO yields as without accurate information FDA is unable to determine if this information causes the new product to raise different questions of public health.

4. Your SE Report includes inconsistencies in the target specifications of several design parameters when comparing your December 2017 amendment to your earlier amendments. You state that the target specifications have been updated since the previous amendments and indicate that differences in the values are due to reporting errors that you have noted or to the rounding to different significant figures between amendments. Furthermore, the parameter values have changed across multiple amendments, which indicates that the error is likely to be attributable to reporting mistakes. If the remanufactured predicate product test data cannot be extrapolated to the predicate product, FDA is unable to determine whether the new product has different design parameters than the predicate product.

   Therefore, you needed to clarify the inconsistencies in the design parameter target specifications and upper and lower range limits provided in the December 2017 amendment compared to those provided in the original SE Report and earlier amendments, as indicated below:

   a. Target specification and upper and lower range limits
      i. Tobacco filler mass (new product)
      ii. Tobacco rod density (new product)
   b. Target specification
      i. Filter total denier (new and predicate products)
      ii. Filter denier per filament (new and predicate products)
      iii. Filter density (new and predicate products)

   c. Upper and lower range limits
      i. Tobacco rod density (predicate product)
      ii. Cigarette paper base paper basis weight (new product)
      iii. Cigarette paper base paper porosity (new product)

a. Cigarette draw resistance (new product)
b. Tobacco filler mass (new product)
c. Tobacco rod density (new product)
d. Cigarette paper band porosity (predicate product)
e. Filter density (new and predicate products)

Target specification

a. Cigarette paper base paper basis weight (predicate product)
b. Filter total denier (new and predicate products)
c. Filter denier per filament (new and predicate products)

Upper and lower range limits

h. Tobacco rod density (predicate product)
i. Cigarette paper base paper porosity (new and predicate products)
j. Filter total denier (new and predicate products)
k. Filter ventilation (new product)

Additionally, differences in design parameters between the new and predicate tobacco products may cause the new product to raise different questions of public health. Therefore, you needed to provide scientific justification for why the differences to cigarette draw resistance and cigarette paper band space between the new and predicate tobacco products do not cause the new product to raise different questions of public health.

6. Your SE Report provides the target specifications and upper and lower range limits for cigarette paper band diffusivity, but not for cigarette paper band porosity for the new product. Additionally, you provide the target specifications and upper and lower range limits for cigarette paper band porosity, but not for cigarette paper band diffusivity for the predicate product. Band porosity and band diffusivity are not identical parameters and are not interchangeably used. Diffusivity mimics air flow during smoldering and is mainly used for predicting cigarette burn rates. Band porosity measures air permeability, allowing for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. The measurement of cigarette paper band porosity thereby relates directly to TNCO exposure. Furthermore, since band porosity allows for the overall assessment of the change in air flow, band porosity information is needed to adequately characterize the new products. In addition, you do not provide a correlation between diffusivity and porosity to allow for a scientific comparison and evaluation of how the two design parameters can be extrapolated to one another. You did provide a study performed by your cigarette paper material supplier, however this study does not demonstrate a means to correlate cigarette paper band porosity to cigarette paper band diffusivity. However, without the target specifications and upper and lower range limits for either (a) cigarette paper band porosity for the new product or (b) cigarette paper band diffusivity for the predicate product, a comparison cannot be made between the new and predicate tobacco products. Differences to cigarette paper band porosity may influence the burn characteristics of the cigarette, as well as air flow through the tobacco column, which may cause the new products to raise different questions of public health. Therefore, you needed to provide either the target specifications and upper and lower range limits for cigarette paper band porosity for the new product or the target specifications and upper and lower range limits for cigarette paper band diffusivity for the predicate product. If a difference in

cigarette paper band porosity exists between the new and predicate tobacco products, you needed to provide a rationale for each difference in the target specification with evidence and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

Additionally, the certificate of analysis (COAs) for cigarette paper band porosity does not include the target specification and upper and lower range limits for cigarette paper band porosity for the new and predicate product. COAs are used to confirm whether design parameters have been met must include the target specification; quantitative acceptance criteria; parameter units; test data average value; and the minimum and maximum values of the test data. The COA should be a complete, unaltered certificate of analysis from the material supplier. Without the target specifications and upper and lower range limits, the COAs cannot be used to confirm whether the specifications for cigarette paper band porosity have been met for the new product. You needed to provide complete COAs for cigarette paper band porosity for the new and predicate products.

7. Your SE Report includes specifications for tobacco filler mass and filter density for the predicate product, but does not include test data sufficient to confirm that the specifications are met. Test data are measured values of design parameters and include test protocols, quantitative acceptance criteria, data sets, and a summary of the results. You provide design parameter test data from the remanufactured predicate product to be extrapolated to the predicate product, but the remanufactured predicate product test data cannot be extrapolated to the predicate products due to inconsistencies in the values of design parameters among your amendments. Therefore, you needed to provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results or unaltered material supplier COA (including the design parameter target specification, quantitative acceptance criteria, parameter units, test data average value, and the minimum and maximum values of the test data) for the tobacco filler mass and filter density for the predicate product. For each of the above parameters, you also needed to provide the necessary data on a per unit of measurement of product basis (e.g., tobacco filler mass should be reported in mg per cigarette). FDA is unable to make a comparison between the new product and the predicate product because the surrogate predicate product cannot be extrapolated to the predicate product for the provided engineering parameters.

8. Your SE Report indicates that the puff count of the new product is higher than the puff count of the predicate product in your December 2017 amendment. Additionally, for the new product, the puff count test data you provided in response to the December 2017 amendment are inconsistent with the puff count test data you provided in earlier amendments. An increase in puff count may increase smoke constituent yields, causing the new product to raise different questions of public health. Therefore, you needed to clarify the inconsistency in the puff count test data among the amendments for the new product. Additionally, you needed to provide a scientific rationale for why the increase in puff count does not cause the new product to raise different questions of public health.

9. Your SE Report indicates that (b) (4) [redacted] increased and (b) (4) [redacted] was added in the new product compared to the predicate product. These ingredients have the potential to change the smoke profile by being directly transferred to the cigarette smoke without

structural changes through distillation/volatilization during smoking. However, you did not provide sufficient evidence to support that these ingredient increase does not cause the new product to raise different questions of public health. You needed to provide scientific evidence and rationale explaining why the increase in quantity of this ingredient does not cause the new product to raise different questions of public health. One way you may have satisfied this concern is by providing a rationale explaining how data generated using the experimental cigarettes evaluated in referenced scientific studies can be extrapolated to the new and predicate products, taking into account cigarette composition and smoke dilution methods. If you eleceted to do so, you would have needed to explain how data extrapolated from such references supports the conclusion that the different characteristics in your new product as compared to the predicate product does not cause the new product to raise different questions of public health.

10. Your SE Report includes a voluntarily submitted quantitative risk assessment (QRA) and probabilistic risk assessment (PRA) to support the position that the changes in tobaccos and tobacco ingredients, and increases in multiple HPHC levels do not cause the new products to raise different questions of public health. Your SE Report includes data comparing the quantities of HPHCs in tobacco filler in the new and remanufactured predicate product. The ammonia and NNN yields in the new product are 40% and 14% higher, respectively, than the remanufactured predicate products. Additionally, the new product shows a 30% increased NNK and a 35% increased NNN yield under ISO smoking conditions and a 33% increased NNK and a 16% increased NNN yield under Cl smoking conditions. The submitted QRA/PRA, did not provide key information needed to evaluate the HPHC changes between the new and predicate products.

    The data, results, and analysis of the QRAs and PRAs provided are either unclear or lack sufficient details to enable FDA to evaluate whether the changes in tobaccos and tobacco ingredients and increases in multiple HPHCs do not cause the product to raise different questions of public health. Thus, to the extent you provided a QRA/PRA for the purpose of demonstrating that such differences do not cause the new product to raise different questions of public health, you needed to address the following issues and supply additional information:

    a. Additional information on how the cumulative HQ and cumulative ILCR values were calculated, including 1) which HPHCs were included in the calculation of the cumulative values, 2) justification for the smoke HPHCs included, 3) detailed description of each calculation, 4) a scientific rationale for not assessing cumulative hazard or risk in the QRAs and 5) how to interpret the results of the cumulative ILCR and HQ (HI) based on distribution means resulting from the PRAs. If there is any HPHC that is significantly different in an analytically meaningful way in the new product compared to the remanufactured predicate product, but was not included in the calculation of cumulative HQ/cumulative ILCR, an explanation as to how the omission of any HPHC can impact the results of the QRA or PRA is needed.
    b. A detailed explanation of any route-to-route extrapolations, including input data, assumptions, equations and outputs.
    c. A detailed selection criteria for the selection of reference values and scientific evidence for deviating from established reference values. Include additional evidence or rationale for selected reference values, given the availability of multiple

reference values for a specific constituent. Any rationale should include scientific evidence for deviating in methodology from the National Research Council and the Guidelines for Carcinogen Risk Assessment.

d. Evidence that the reference values used in the calculation of the HQ or ILCR, and used in both the QRA and PRA, are appropriate for the toxicological endpoints associated with the use of the new and predicate products.
e. A clear description of how you intend to characterize and interpret the QRA and PRA results. In the 'Problem Formulation' section, you state that "*the risk assessment (i.e., QRA) presented herein does not concern absolute risk or hazard but rather the comparative risk or hazard between the two products (i.e., Subject and Reman Predicate/Predicate).*" However, you provided data and a discussion relating to the absolute risk or hazard (e.g., the total cancer risk or margin-of-exposure).
f. Specific evidence or rationale for the inclusion of body weight and daily inhalation rate in your estimation of exposure concentrations regarding the smoker exposure scenario.
g. Clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime is appropriate for the specific products and user populations.
h. All raw data, equations, assumptions, parameters, outputs, and references used in the QRA and PRA, including the HPHC data, methods used to determine statistical variability and any other pertinent data used in these calculations.
i. A complete description of the PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. For example, although the assumed minimum, maximum and "likeliest" values for the distributions are provided, no justifications for the use of Beta PERT distributions (used for Cigarettes per Day (CpD), Exposure Duration (ED), Averaging Time (AT)) or Gamma distribution (used for Daily Inhalation Rate (DIR)) are given. Provide scientific evidence that the parameter ranges and means are specific to the new and predicate products and the expected user populations. Consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions.
j. Scientific evidence and rationale demonstrating that the distributions for each parameter and the ranges are appropriate given the characteristics of the new and predicate products and the anticipated user population of both products. Any rationale or scientific evidence needs to also include further discussion as to the quality and appropriateness of the inputs as well as the PRA expectations that the resulting parameter estimations accurately reflect the real product or user specific values.
k. Evidence that the daily inhalation parameter used in the reference you cited, Marano et al, 2012, 193.99 L/kg-d, is appropriate for tobacco product-specific exposures as well as the population expected to use the new and predicate products.
l. Sufficient and clear description on several aspects of computational methodology, input parameters, and interpretation of the assessment results. Importantly, the PRA does not address uncertainties inherent to other critical elements in the QRA. In discussing uncertainty and variability, you needed to provide an assessment of the PRA's ability to discern a statistical difference in risk between tobacco products. You

needed to provide sufficient characterization of uncertainties and variation of all other critical elements in risk assessment processes, such as:

i. Uncertainty in the use of addition for estimating total hazard or risk from components of a mixture in which other interactions may occur or the available information indicates combinations other than additivity regarding dose effects and adverse health outcomes.
ii. Uncertainty of representing the total adverse health risks of the new and predicate cigarette products with a small number of constituents selected for the QRA/PRA.