Technical Project Lead (TPL) Review: SE0000276, SE0000277, SE0000278, SE0000281

SE0000276: Camel Crush Bold	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	20%
Characterizing Flavor	Menthol
Additional Property	Crushable menthol capsule in filter
SE0000277: Vantage Tech 13	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	25%
Characterizing Flavor	None
SE0000278: Pall Mall Deep Set Recessed Filter Menthol	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	34%
Characterizing Flavor	Menthol
SE0000281: Pall Mall Deep Set Recessed Filter	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	34%
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	R.J. Reynolds Tobacco Company
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Filtered Combusted
Recommendation	
Issue Not Substantially Equivalent (NSE) Orders.	

Technical Project Lead (TPL):

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Date: 2015.09.11 15:26:56 -04'00'

Matthew R. Holman, Ph.D.
Director
Division of Product Science

Signatory Decision:

☒ Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

Digitally signed by David Ashley -S
Date: 2015.09.11 15:31:13 -04'00'

David L. Ashley, Ph.D.
RADM, U.S. Public Health Service
Director
Office of Science

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1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted the following predicate tobacco products:

SE0000276	**Camel Crush Bold**
Product Name	Kool Filter Kings Box
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	20%
Characterizing Flavor	Menthol
SE0000277	**Vantage Tech 13**
Product Name	Camel Light Hard Pack
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	25%
Characterizing Flavor	None
SE0000278	**Pall Mall Deep Set Recessed Filter Menthol**
Product Name	Salem Lights Green Label Box
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	34%
Characterizing Flavor	Menthol
SE0000281	**Pall Mall Deep Set Recessed Filter**
Product Name	Camel Light Hard Pack
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Filter Ventilation	34%
Characterizing Flavor	None

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

In all of its original SE Reports, the applicant selected, as its predicate tobacco product, a composite of all cigarettes commercially marketed in the United States as of February 15, 2007. On October 25, 2012, FDA sent the applicant an Advice/Information Request Letter (A/I Letter), which stated that the applicant's

SE Reports lacked information to fully identify the predicate tobacco product (i.e., how the predicate tobacco product is uniquely identified for a consumer such as brand, subbrand, size, quantity, and packaging). In November 2012, the applicant restated its position that its predicate tobacco product was a composite of all cigarettes commercially marketed in the United States as of February 15, 2007.

On March 29, 2013, FDA issued a Notification Letter, which informed the applicant that scientific review would commence on May 15, 2013. The Notification Letter further stated that, while FDA will review all amendments received no later than May 14, 2013 (as well as promptly submitted solicited amendments), FDA is not obligated to review unsolicited amendments and FDA's general practice is not to consider such amendments received after scientific review commences while FDA determines whether the new tobacco product is substantially equivalent. In response to the Notification Letter, on May 14, 2013, the applicant amended its SE Reports, replacing the composite predicate tobacco products with uniquely identified predicate tobacco products for each of the SE Reports. For SE0000276, the applicant identified the predicate tobacco product as Kool Filter Kings Box.

On March 18, 2014, FDA issued an A/I Letter to the applicant; the letter contained deficiencies based on scientific review. In response, the applicant requested an extension of nine months to respond to the A/I Letter. The extension request stated that the applicant believed, for SE0000276, Camel Light Box with Menthol Capsule is the most appropriate predicate tobacco product, and, therefore, an extension was needed so that the applicant could provide additional information on that product. The Camel Light Box with Menthol Capsule product, however, was not identified in the original SE Report and was not identified by the applicant as the predicate tobacco product when the applicant amended its SE Report prior to the start of scientific review in May 2013.[1]

Because the comparison between the new tobacco product and the identified predicate tobacco product is a fundamental aspect of an SE Report, changing the predicate tobacco product changes the basis for the analysis. FDA is not obligated to review unsolicited amendments and FDA's general practice is not to consider such amendments received after scientific review commences while FDA determines whether the new tobacco product is substantially equivalent. The application review is based on the comparison between the predicate

[1] In response to the A/I Letter, the applicant contended that it was not aware that it could identify a predicate tobacco product that had not yet received a grandfathered determination prior to commencing scientific review. The grandfathered determination for the Camel Light Box with Menthol Capsule product was not received by the applicant until May 24, 2013. However, the original predicate tobacco product identified by the applicant did not have grandfathered determination, as it was a composite of all cigarettes commercially marketed in the United States as of February 15, 2007.

tobacco product in place at the start of scientific review and the new tobacco product.

This information was communicated to the applicant in two letters dated May 9, 2014. The correspondence further informed the applicant that, if the applicant would like to use a different predicate tobacco product, the applicant could submit new SE Reports. The applicant did not submit new SE Reports. Notwithstanding the May 9, 2014, correspondence, in its April 2015 amendment (responding to the March 3, 2015, Preliminary Finding Letter), the applicant nevertheless provided information for Camel Light Box with Menthol Capsule.

Because Camel Light Box with Menthol Capsule was not identified as a predicate tobacco product when scientific review commenced, information relating to that product was not considered during FDA's review of the SE Reports. If the applicant would like to use a different predicate tobacco product than that identified at the time scientific review commenced, then, as FDA had communicated to the applicant in May 2014, the applicant will need to submit new SE Reports.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 18, 2011, the applicant submitted the 4 provisional SE Reports. FDA issued an Advice/Information Request Letter (A/I Letter) on October 25, 2012. In response, the applicant submitted an amendment on November 16, 2012. FDA issued a Notification Letter on March 29, 2013[2], indicating that scientific review would begin on May 15, 2013. In response, the applicant submitted an amendment on May 14, 2013. After reviewing the amendment, FDA issued an A/I Letter on March 18, 2014. In response, the applicant submitted an amendment (SE0010324), which requested an extension of nine months to respond to the A/I Letter. FDA issued an Extension Clarification letter on March 26, 2014, explaining to the applicant the required information that should be submitted with a request for an extension (e.g., rationale for request). The applicant submitted an amendment in response (SE0010361) on April 2, 2014. FDA issued an Extension Denial Letter on May 9, 2014. The applicant submitted an amendment on May 16, 2014 (SE0010497), in response to the March 2014 A/I Letter. After reviewing the amendment, FDA issued a Preliminary Finding Letter on March 3, 2015. The applicant submitted an amendment (SE0010952) on March 6, 2015, requesting an extension of time to respond to the Preliminary Finding Letter. FDA issued an Extension Denial letter on March 31, 2015. In response, the applicant submitted an amendment (SE0011106) on April 2, 2015 responding to the March 3, 2015, Preliminary Finding letter.

[2] It should be noted that a correction letter was issued on April 5, 2013, to correct instructions regarding how to respond to the Notification Letter. The correction letter did not alter the date for beginning scientific review.

Product Name	SE Report	Amendments
Camel Crush Bold	SE0000276	SE0005103 SE0008568 SE0010324 SE0010361 SE0010497 SE0010952 SE0011106
Vantage Tech 13	SE0000277	SE0005104 SE0008550 SE0010324 SE0010361 SE0010497 SE0010952 SE0011106
Pall Mall Deep Set Recessed Filter Menthol	SE0000278	SE0005105 SE0008569 SE0010324 SE0010361 SE0010497 SE0010952 SE0011106
Pall Mall Deep Set Recessed Filter	SE0000281	SE0005108 SE0008567 SE0010324 SE0010361 SE0010497 SE0010952 SE0011106

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 October 25, 2012, and December 20, 2012.

The final reviews conclude that the 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 identified in

the applicant's May 14, 2013, amendment are grandfathered products (i.e., were commercially marketed as of February 15, 2007). The OCE reviews dated May 22, 23, and 29, 2013, 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.

Because the new tobacco products are not substantially equivalent to the predicate tobacco products, OCE did not complete reviews to determine whether the new tobacco products are in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as required by section 910(a)(2)(A)(i)(II) of the FD&C Act.

4. SCIENTIFIC REVIEW

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

4.1. CHEMISTRY

Chemistry reviews were completed by Jianping Gong on September 18, 2013, by Thomas Eads on August 14, 2014, and by Timothy Brewer on May 27, 2015.

The final chemistry review concludes that the new tobacco products have different characteristics related to product composition compared to the corresponding predicate tobacco products and that the SE Reports do not contain sufficient detail to determine that those differences with respect to product composition 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. In SE0000276, your response to Deficiency 11 in your April 2015 amendment provided information demonstrating that the new product contains significantly more menthol than the predicate product. However, you did not provide standard deviation associated with the measurements of extracted menthol from the cigarette, presumably because only two replicates were tested. Provide sufficient information, including the number of replicates and the mean and standard deviation for extracted menthol, so that FDA can evaluate the statistical significance of differences in menthol levels between the new and predicate products.

2. In your April 2015 amendments to SE0000278 and SE0000281, you report that you changed the tobacco blends for the new products on (b) (4) It is unclear whether HPHC data you've provided for the new products is for the (b) (4) (b) (4) formulation. Clarify whether the HPHC data you provided for the new products in SE0000278 and SE0000281 is for the (b) (4) formulation.

3. All of your SE Reports list tobacco blend quantities as percentages but do not specify the original units of the numerator and denominator, or define the denominator. For SE0000278 and SE0000281, you also provided tobacco blend quantities in units of mg/cigarette for the predicate products and for the (b) (4) formulation of the new products. In order for us to fully understand the composition of the new and predicate products and make a determination of substantial equivalence, provide tobacco blend quantities as mass per unit of use (e.g., mg/cigarette) for the new and corresponding predicate products in SE0000276 and SE0000277, and for the (b) (4) formulation for the new products in SE0000278 and SE0000281.

Therefore, the review concludes that there was inadequate information from a chemistry perspective to determine 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.

The final chemistry review concludes that the applicant adequately addressed Deficiency 8 from the March 2015 Preliminary Finding Letter:

> In SE0000276, SE0000278, and SE0000281, your response to Deficiency 12 of the March 2014 Scientific A/I letter provided a literature summary regarding effects of sugars on smoke constituents. You also provided a comparison of HPHC values to account for between-replicate and between-manufacturing run variation in your response to Deficiency 22 of the March 2014 scientific A/I letter. However, the comparison does not include sufficient detail for FDA to fully evaluate the information provided. Provide a full description of the origins of HPHC data, statistical tests applied, values for standard deviations derived from the RJRT internal product variation study, values for any other variances used in the statistical tests, explanation and justification of any assumptions applied, and distinguish clearly between HPHC values from between-replicate and between-run measurements.

It should be clarified that the chemistry review only evaluated whether the applicant provided sufficient information about HPHC testing to allow FDA to determine whether the results are accurate and reliable. The review concludes that the applicant has demonstrated that results are accurate and reliable. It should also be clarified that it is not clear which tobacco blend was used in the tested cigarettes (see below). The conclusion of the chemistry review is not impacted by the tobacco blend used in the tested cigarettes because, for example, the blend does not affect the analytical methods that need to be used and does not impact the statistical analysis of the data. However, the review indicates that the toxicology review will evaluate the between-run variability (derived from the HPHC testing). The toxicology review did, in fact, evaluate the HPHC data. More specifically, the toxicology review evaluated of the

Quantitative Risk Assessment (QRA) submitted by the applicant in an effort to explain why the increases in HPHC yields do not cause the new tobacco products to raise different questions of public health [see section 4.3 of this review].

It should also be noted that the final chemistry review indicates that there is an error in the September 18, 2013, chemistry review regarding the units of measurement for the tobacco blend quantities. The September 18, 2013, chemistry review reported tobacco quantities in milligrams per cigarette, but the quantities included in the review were actually percentages. This error does not alter the overall conclusion of the final chemistry review (i.e., there is inadequate information from a chemistry perspective to determine 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). However, this error led to the inclusion of Deficiency 3 in the final chemistry review; if the error was not made, Deficiency 3 would have been included in the September 18, 2013, chemistry review instead of the final chemistry review. Deficiency 3 from the final chemistry review should be conveyed to the applicant but this deficiency does not form the basis for the finding of Not Substantially Equivalent (NSE).

Finally, it should be made clear that the new tobacco products that are the subjects of SE0000278 and SE0000281 contain the (b) (4) blend. Deficiencies seeking information related to the (b) (4) blend were only included in order to compare the blends to determine whether HPHC data for the (b) (4) blend can be extrapolated to the (b) (4) blend. Nevertheless, given that the applicant did not provide sufficient information to determine which blend was even tested, the foregoing information would not resolve these deficiencies. Therefore, the deficiencies should be revised to exclude any reference to the (b) (4) tobacco blend.

4.2. ENGINEERING

Engineering reviews were completed by Komal Ahuja on September 9, 2013, August 14, 2014, and May 21, 2015.

The final engineering review concludes that the new tobacco products have different characteristics related to product design compared to the corresponding predicate tobacco products and that the SE Reports do not contain sufficient detail to determine that those differences with respect to product engineering 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. All of your SE Reports provide information on some of the target specifications and upper and lower range limits. The following additional information is required in order to adequately characterize your products:

    a. You provide target specifications and range limits for cigarette paper band diffusivity for the new and predicate products and cigarette paper band porosity for the predicate products. However, you did not provide a correlation between diffusivity and porosity to allow for a scientific comparison and evaluation. Therefore, measure and report target specifications and upper and lower range limits for cigarette paper band porosity (CU) for each new product.
    b. You provide some of the range limits for filter total denier, denier per filament, and density. However, you do not provide all of the information necessary to adequately characterize your products and evaluate your test data. Provide the upper and lower range limits for filter total denier and denier per filament.

    For the parameters above, if a difference exists between the new and corresponding predicate products, provide a rationale for each difference in the target specification and range limits with evidence and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

2. All your SE Reports provide test data for some of the parameters. However, you do not submit all of the necessary testing information to confirm the target specifications are met. In order to fully evaluate whether or not the target specifications are met, you must submit the following information:

    a. Provide the full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for each new and predicate product for filter density, filter total denier, filter denier per filament, and plug wrap length.
    b. Provide the test protocols for cigarette paper band porosity for each new and predicate product and the quantitative acceptance criteria for the new products.

c. You supply only summary data, not complete data sets, for cigarette paper base paper basis weight, cigarette paper base paper porosity, and cigarette paper band porosity for each new product and for the predicate products in SE0000276, SE0000277, and SE0000281; and plug wrap basis weight for each predicate product. In order to fully evaluate whether or not the target specifications are met, provide the data sets for all of the new and predicate products, in addition to the summarized data, for cigarette paper base paper basis weight and cigarette paper base paper porosity. Provide the data sets for all of the new products and for the predicate products in SE0000276, SE0000277, and SE0000281 for cigarette paper band porosity. Provide the data sets for all of the predicate products, in addition to the summarized data, for plug wrap basis weight.

Certificates of analysis from the material supplier may satisfy this deficiency. If you choose to address this deficiency by providing certificates of analysis for any of the parameters listed above, the certificates of analysis must include a target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data. 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.

3. In SE0000276, you explain that the cigarette draw resistance target specifications are adjusted if the manufacturing data is resulting in an increasing or decreasing trend. (b) (4) Therefore, the target specification reported to the FDA was not consistent with the specification in place at the time of the production data that was submitted. However, the target specification should provide the exact manufacturing standard to which each design parameter must conform. The range limits characterize the product based on the target specifications and product attributes (e.g., taste, use, and HPHC limits). Test data demonstrate if the product conforms to the standards. When manufacturing data does not fall within the range limits of the specification, it is an indication that deviations are occurring (e.g., raw materials are out of specification, equipment malfunction, etc.). By changing the target specification on a continuous basis to meet the production data, the target specification is no longer representing the product characteristics. Therefore, provide a rationale for this process to

demonstrate that shifting the target specification for cigarette draw resistance has not created a difference in the product characteristics. Furthermore, provide a revised procedure to ensure future target specifications will not be altered based on trending data alone.

4. In SE0000277, SE0000278, and SE0000281, you confirm the upper and lower range limits provided in the amendment from May 16, 2014 are the correct values for filter pressure drop in the new products. You explained that the filter rods are manufactured independently of the cigarettes and in turn may have different range limits compared to the individual filter segments that are subject to further manufacturing and incorporated into the cigarette. The supplier's COA illustrates the filter rod, not the filter segment. However, your rationale is based on the length difference between a rod and a segment, stating that as a result of the variability when the rod is cut, your ranges are slightly wider than the supplier's ranges. It is unclear how the filter segment lengths vary when the cutting process is precise to (b) (4). Furthermore, if the filter length ranges are tight, the filter pressure drop ranges should mimic closely. Typically, the filter segment pressure drop is very similar, if not equal, to the filter rod pressure drop when divided by the cut number. You have not justified how the segment length difference translates into the pressure drop difference apparent between your range limits and the supplier's. Provide a clear rationale with scientific justification, including evidence, that the filter segments result in wider segment pressure drop ranges than the rod pressure drop ranges.

Therefore, the review concludes that there was inadequate information from an engineering perspective to determine 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.

4.3. TOXICOLOGY

Toxicology reviews were completed by Brian Erkkila on March 13, 2014, and February 9, 2015, and by Lynn Crosby on July 16, 2015.

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 do not contain sufficient detail to determine that those differences with respect to product toxicology 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. SE0000276, SE0000278, and SE0000281 list ingredients in the new products that are not present in the corresponding predicate products:

    - SE0000276: (b) (4)
    - SE0000278 and SE0000281: (b) (4)

    The literature submitted to support these ingredient additions used cigarettes that are very different from either the new or predicate products and therefore do not adequately address a substantial equivalence comparison between the new and predicate products. Ingredients in this literature were tested in experimental cigarettes containing mixtures of multiple ingredients, many times more than 100 ingredients, and not the same or similar to the ingredient mixtures present in either the new or predicate products. The GRAS designation of these ingredients cannot inform the substantial equivalence comparison because GRAS does not apply to tobacco products and does not apply to the inhalation route. The contention that these ingredient changes did not increase HPHC deliveries in the new products as compared to the predicate products cannot be ruled out because analysis of submitted raw data on the new and predicate products indicates that HPHC deliveries did in fact increase in the new products relative to the corresponding predicate products. Therefore, these ingredient changes may cause the new products to raise different questions of public health.

2. All of your SE Reports provide a Quantitative Risk Assessment (QRA) which you claim demonstrates that the HPHC increases in the new products do not raise different questions of public health. While a QRA is not required for a substantial equivalence evaluation, such an analysis could potentially provide useful information. However, the submitted QRA could not inform the substantial equivalence comparison between the new and predicate products for the following reasons:

    - The HPHC delivery values for the new and predicate products on which the QRA is based contained estimates of statistical variation

that were derived from the HPHC results from >100 cigarette brands that are neither the new or predicate products and no evidence was provided which demonstrates the equivalence of these results and the results for the new and predicate products.

- The HPHC comparisons in the QRA combined HPHC data that used the ISO smoking regimen for some HPHCs and the CI smoking regimen for other HPHCs, resulting in the summing of calculated risks based on different analytical methods.
- The QRA did not use important inhalation dosimetry parameters such as those listed in the updated USEPA RAGS F guideline. In addition, SE0000278 and SE0000281 indicate that the HPHC data which forms the basis for the QRA was generated from cigarettes produced after the (b) (4) blend change. As a result, for SE0000278 and SE0000281, the QRA does not apply to the relevant original new products listed in these SE Reports.

Therefore, the QRA submitted in SE0000276, SE0000277, SE0000278, and SE0000281 does not adequately demonstrate that increased levels of HPHCs do not cause the new products to raise different questions of public health. The HPHC delivery increases observed in the new products relative to the corresponding predicate products cause the new products to raise different questions of public health.

Therefore, the review concludes that there was inadequate information from a toxicology perspective to determine 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.

It should be noted that, as specified in the last bulleted statement in Deficiency 2, the QRAs for the new and predicate tobacco products in SE0000278 and SE0000281 were based on data from cigarettes produced after the (b) (4) blend change. However, the chemistry review indicates that it is unclear what tobacco blend was used in the cigarettes that were analyzed for HPHC yields. I am not certain why the chemistry and toxicology reviewers had different understanding of the tested products, but it appears that the toxicology reviewer may have assumed the (b) (4) - (b) (4) blends were used in tested products because the manufacturing dates of the tested products and the test dates occurred after (b) (4) Regardless of whether the analyzed cigarettes were produced after the (b) (4) blend change (as indicated in the toxicology review) or whether the blend of the analyzed cigarettes was unknown (as indicated in the chemistry review), the conclusion of the toxicology review is the same for SE0000278 and SE0000281; the QRAs are not adequate for demonstration of substantial equivalence for the reasons listed in Deficiency 2.

Revisions to Deficiency 1 would help clarify the issues conveyed in the deficiency. GRAS designations apply to food products that are ingested. As

such, the deficiency should state that cigarettes are not food products and not intended for ingestion, and, therefore, the fact that ingredients in Deficiency 1 have been designated GRAS for food does not necessarily mean that they are safe for inhalation. In addition, the sentence that reads, "The contention that these ingredient changes did not increase HPHC deliveries in the new products as compared to the predicate products cannot be ruled out because analysis of submitted raw data on the new and predicate products indicates that HPHC deliveries did in fact increase in the new products relative to the corresponding predicate products" should be revised to indicate that the applicant's contention that addition of the ingredients in Deficiency 1 to the new tobacco products does not significantly change HPHC yields cannot be confirmed because of the issues described in Deficiency 2 for the applicant's HPHC analysis and QRA.

The last sentence in Deficiency 2 should not be conveyed to the applicant in the order letters. The sentence states that the increased HPHC yields in the new tobacco products compared to the corresponding predicate tobacco products cause the new tobacco products to raise different questions of public health. However, the preceding sentence in Deficiency 2 states that there is insufficient information in order to determine whether the increased HPHC yields cause the new tobacco products to raise different questions of public health. This sentence is consistent with the conclusion of the final toxicology review (page 29); the toxicology review does not conclude that the new tobacco products raise different questions of public health.

4.4. SOCIAL SCIENCE

Social science reviews were completed by Amber Koblitz on September 10, 2013, August 14, 2014, and September 11, 2015. In addition, a memorandum[3] was completed by David Portnoy on November 14, 2013.

[3] The memorandum served to provide additional discussion and support for the conclusion in the September 10, 2013, review that additional of the menthol capsule in the filter may cause the new tobacco product in SE0000276 to raise different questions of public health.

The final social science review concludes that the new tobacco products in SE0000277, SE0000278, and SE0000281 have different characteristics compared to the corresponding predicate tobacco products but the differences with respect to consumer perception and its impact on use do not cause the new tobacco products to raise different questions of public health. The final social science review concludes that the new tobacco product in SE0000276 has different characteristics compared to the predicate tobacco product and that the SE Report does not contain sufficient detail to determine that those differences with respect to consumer perception and its impact on use 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. In SE0000276, the most significant difference between the new and predicate tobacco products related to consumer perception and use is the placement of a capsule containing menthol in the filter of the new tobacco product. The new tobacco product's flavor delivery system allows users to choose whether to smoke the new tobacco product with or without menthol, effectively creating an adjustable menthol/non-menthol cigarette. In addition, non-menthol and menthol-smokers can share cigarette packs of the new tobacco product. As a result, this difference in flavor delivery system between the new and predicate tobacco products may influence consumer perception and use by providing users with a novel, versatile flavor delivery system. FDA requested you provide data to support your assertions that the change in flavor delivery system does not impact tobacco perception and use such that the new tobacco product does not raise different questions of public health (see Deficiency 24 from the March 18, 2014 A/I letter and Deficiencies 16 and 18 from the March 3, 2015 Preliminary Finding letter). In your response to the Preliminary Finding letter, you provided a summary of trend data from the (b) (4) [redacted] However, the following issues prevent FDA from reaching the same conclusions as you:

    a. You did a (b) (4) trend analysis from the (b) (4) and stated that overall (b) (4) showed a statistically significant decline during the time period of the (b) (4). Therefore, in this trend analysis, you compared the (b) (4) (b) (4) associated with the new tobacco product against the (b) (4) arguing that introduction of the new tobacco product to the (b) (4) (b) (4) did not detectably change (b) (4)

(b) (4) . However, determination of substantial equivalence is based on comparison of a new tobacco product to a predicate tobacco product, so your comparison of the new tobacco product to the (b) (4) is not appropriate. Furthermore, (b) (4) .

b. You also provided (b) (4) comparing the new tobacco and predicate tobacco products and stated (b) (4) is not different between the two products. However, because there were (b) (4) of the new and predicate tobacco products in the (b) (4) the (b) (4) was not adequately powered to detect differences in (b) (4) between the new and predicate tobacco products. For example, when calculating (b) (4) , you reported a (b) (4) for Kool Filter Kings. A meaningful comparison between products cannot be made because of the (b) (4) Because of the (b) (4) (b) (4) (b) (4) , statistical analyses and estimates are likely unreliable.

Therefore, the review concludes that there was inadequate information from a social science perspective to determine that the differences in characteristics between the new and predicate tobacco products in SE0000276 do not cause the new tobacco product to raise different questions of public health.

The social science reviews also evaluated the health information summary. The applicant review originally submitted a health information summary. The first social science review concluded that the health information summary potentially violated section 911 of the FD&C Act.[4] In response to the March 18, 2014, A/I Letter, the applicant rescinded the health information summary, indicating that it would provide such information upon request by any party. Therefore, the final review did not identify a deficiency related to the health information summary.

[4] The March 18, 2014 A/I Letter stated in Deficiency 23 that the submitted Health Information Summary may be a violation of section 911(b)(2)(A)(i)(II) of the FD&C Act. Deficiency 23 should have stated, however, that the submitted Health Information Summary may potentially violate section 911(b)(2)(A)(iii) of the FD&C Act.

4.5. ADDICTION

Addiction reviews[5] for SE0000277, SE0000278, and SE0000281 were completed by Maocheng (Tony) Yang on September 4, 2013. An addiction review[5] for SE0000276 was completed by Sarah Evans on September 10, 2013. A clinical pharmacology[6] review was completed by Megan Schroeder on August 20, 2014. Behavioral pharmacology[7] reviews were completed by Sarah Evans on August 29, 2014,[8] and by Kia Jackson on June 5, 2015. In addition, a memorandum[9] re-examining the June 5, 2015, review was completed by Chad Reissig on September 11, 2015.

The final clinical pharmacology review concludes that the new tobacco products have different characteristics compared to the corresponding predicate tobacco products but those differences do not cause the new tobacco products to raise different questions of public health related to clinical pharmacology.

The final behavioral pharmacology review concludes that the new tobacco products (other than SE0000277) have different characteristics compared to their corresponding predicate tobacco products and that the SE Reports do not contain sufficient detail to determine that those differences with respect to consumer use of the product and its impact on behavior do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies,[10] which have *not* been adequately resolved:

1. SE0000276 includes a new product that has a different flavor than the predicate product due to the following differences between the products:

    - Sweeteners and other flavors
    - Menthol levels

    Data that you submitted in your March 2015 amendment demonstrates an increase in menthol smoke yields by (b) (4) under the CI smoking regimen

[5] Each of these reviews addressed both clinical pharmacology and behavioral pharmacology within the review. However, in subsequent scientific review cycles, separate reviews were done for clinical pharmacology and behavioral pharmacology in order to more clearly address these separate but related scientific disciplines relevant to addiction.
[6] Clinical pharmacology reviews evaluate how the new and predicate tobacco products influence the pharmacokinetics/pharmacodynamics of nicotine or other constituents relevant to addiction.
[7] Behavioral pharmacology reviews evaluate how the new and predicate tobacco products influence how consumers use the product and that use's impact on behavior generally associated with addiction (e.g., initiation and cessation) by users and non-users.
[8] It should be noted that Allison Hoffman filed a memorandum on February 27, 2015, to correct the identification of the SE Reports evaluated in the August 29, 2014, review.
[9] At my request, Chad Reissig re-reviewed the June 5, 2015, behavioral pharmacology review to address inaccuracies. After re-reviewing, Dr. Reissig drafted a memorandum to correct these inaccuracies and, as a result, both deficiencies were revised from the original June 5, 2015, review.
[10] Deficiencies 1 and 2 included in this TPL review reflect the text found in the September 11, 2015, memorandum.

and (b) (4) under the ISO smoking regimen in the new product compared to the predicate product. In addition, according to your SE Report, you also add sweeteners and other flavors (e.g., brown sugar) to the new product. Differences in sugars and flavors in cigarettes can mitigate their aversiveness and enhance product appeal (Cummings, Morley, Horan, Steger, & Leavell, 2002). For example, adding flavors and sweeteners may increase the product's palatability, which influences abuse liability (Carter et al., 2009; Henningfield, Hatsukami, Zeller, & Peters, 2011) and may influence initiation behaviors, tobacco dependence, and continued use (Farley, Seoh, Sacks, & Johns, 2014; Henningfield et al., 2011; Villanti, Richardson, Vallone, & Rath, 2013). The increase in menthol yield in the new product may increase the likelihood of initiation and progression to regular use, increase level/severity of dependence, and/or decrease likelihood of cessation success (e.g., (Ahijevych & Garrett, 2010; Foulds, Hooper, Pletcher, & Okuyemi, 2010; Hersey, Nonnemaker, & Homsi, 2010; Hoffman & Miceli, 2011; Hoffman & Simmons, 2011; Rock, Davis, Thorne, Asman, & Caraballo, 2010; Smith, Fiore, & Baker, 2014).

You state that the (b) (4) data demonstrate that the differences in sweeteners and other flavors and menthol levels between Camel Crush Bold and Kool Filter Kings Box do not cause the new tobacco product to raise different questions of public health. However, after consultation with the Social Science reviewer, we have determined the (b) (4) data provided by the applicant are not sufficient. Specifically, given the (b) (4) the new and predicate products in the (b) (4) and (b) (4) . Therefore, provide evidence that the differences in sweeteners and menthol levels (e.g., (b) (4) and (b) (4) increase in menthol yields) between the new and predicate products do not cause the new products to raise different questions of public health.

2. SE0000278 and SE0000281 include new products that have different flavors than the corresponding predicate products due to differences in sweeteners and other flavors. Your March 2015 amendment states that the (b) (4) results demonstrate that there are no differences between the new products Pall Mall Deep Set Recessed Filter and Pall Mall Deep Set Recessed Filter Menthol cigarettes and the corresponding predicate products. Data from the (b) (4) survey during the (b) (4) period of assessments for the new products include (b) (4) of Pall Mall Deep Set Recessed Filter, and (b) (4) (b) (4) Pall Mall Deep Set Recessed Filter Menthol (b)(4) . In addition, there was no information provided specifically about use of the predicate products; the new tobacco products were compared to all other marketed cigarettes. (b) (4) and information about the predicate products was not provided, there are insufficient data to compare the new products to the corresponding predicate products

using the (b) (4) survey. Provide evidence as to why the differences between the new and predicate products do not cause the new products to raise different questions of public health.

Therefore, the review concludes that there was inadequate information from behavioral pharmacology perspective to determine that the differences noted above between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health. As noted in the review, this conclusion is also based on the determination that there is inadequate information to demonstrate that the introduction of the novel flavor delivery system (i.e., addition of a menthol capsule in the filter) does not cause the new tobacco product to raise different questions of public health from a behavioral pharmacology perspective. The review does not include a deficiency related to this product characteristic but defers to the social science review to capture the deficiency (see section 4.4 of this review for the deficiency).

The first deficiency in the behavioral pharmacology review and the deficiency in the social science review (see Section 4.4. of this review) overlap somewhat in content. The behavioral pharmacology deficiency addresses the flavor differences (i.e., taste differences) between the new and predicate tobacco products. The social science deficiency addresses the flavor delivery system differences (i.e., addition of menthol-containing capsule) between the new and predicate tobacco products. The information contained in these reviews, regardless of whether that information was analyzed from the perspective of behavioral pharmacology or social science, shows that these differences between the new and predicate tobacco products can influence initiation, cessation, dependence, continued use, abuse liability, and perception. The applicant relies on the (b) (4) survey to support its assertion that the flavor differences and the flavor delivery system differences do not cause the new tobacco product to raise different questions of public health. However, for the reasons described above, the (b) (4) survey data provided by the applicant is inadequate to show that these differences do not cause the new tobacco product to raise different questions of public health.

5. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by RADM David L. Ashley on November 19, 2013. The FONSI was supported by an environmental assessment prepared by FDA on November 14, 2013.

6. CONCLUSION AND RECOMMENDATION

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

- Higher menthol smoke yields [SE0000276]
- Different characterizing flavor delivery method (menthol capsule in the filter compared to menthol in tobacco filler) [SE0000276]
- Addition of (b) (4) particles in the filter [SE0000277]
- Filter recessed in plug wrap/tipping paper (compared to non-recessed filter) [SE0000278 and SE0000281]
- Differences in sugars and flavors [SE0000276, SE0000278, and SE0000281]
- Addition of (b) (4) [SE0000276]
- Addition of (b) (4) [SE0000278 and SE0000281]
- Increased smoke yields for numerous HPHCs

There may be other key differences in characteristics between the new and corresponding predicate tobacco products that could not be identified because of insufficient information about some of the product characteristics. All of the scientific reviews conclude that some of the differences in characteristics do not cause the new tobacco products to raise different questions of public. It should be noted that all of the scientific reviews and this TPL review consider the new tobacco products to be those containing the tobacco blend used prior to (b) (4) and compared these new tobacco products to the predicate tobacco products in place at the start of scientific review. All of the scientific reviews except clinical pharmacology conclude that at least one difference in product characteristics may cause the new tobacco products to raise different questions of public health from their respective discipline perspective. I concur with the reviews that the applicant has failed to provide sufficient information to demonstrate that these differences in characteristics do not cause the new tobacco products to raise different questions of public health.

The predicate tobacco products meet statutory requirements because they are grandfathered products (i.e., were commercially marketed in the United States as of February 15, 2007).

FDA examined the environmental effects of finding these new tobacco products not substantially equivalent and made a finding of no significant impact.

NSE orders letter should be issued for the new tobacco products in SE0000276, SE0000277, SE0000278, and SE0000281, as identified on the cover page of this review. The NSE order letters should include the deficiencies identified in the

scientific reviews. Additionally, **prior** to the list of deficiencies for SE0000276, the following text should be inserted:

> Your SE Report includes information for an additional tobacco product (Camel Light Box with Menthol Capsule) that you identified in your April 2015 amendment as a predicate tobacco product. Information for this additional tobacco product is provided alongside information for the predicate tobacco product identified in the SE Report at the time scientific review commenced. Because the comparison between the new tobacco product and the identified predicate tobacco product is a fundamental aspect of an SE Report, changing the predicate tobacco product changes the basis of the substantial equivalence evaluation. FDA is not obligated to review unsolicited amendments and FDA's general practice is not to consider such amendments received after scientific review commences while FDA determines whether the new tobacco product is substantially equivalent. You were issued a Notification Letter on March 29, 2013, which notified you that scientific review was scheduled to begin on May 15, 2013; therefore, you had the opportunity to change your predicate tobacco product up to May 14, 2013. You provided an amendment on May 14, 2013, which identified Kool Filter Kings Box as your predicate tobacco product, and review was based on the comparison between the predicate tobacco product in place at the start of scientific review and the new tobacco product. Therefore, Camel Light Box with Menthol Capsule was not considered in our evaluation of your SE Report. The deficiencies listed in this letter reflect a comparison of the new tobacco product against the predicate tobacco product in place at the start of scientific review, Kool Filter Kings Box.

6.1. DEFICIENCIES FOR SE0000276

The NSE order letter for SE0000276 should cite the following deficiencies:

1. Your April 2015 amendment provides information demonstrating that the new tobacco product contains significantly more menthol than the predicate tobacco product. However, your SE Report does not provide standard deviation associated with the menthol measurements. In order for FDA to evaluate the statistical significance of differences in menthol levels between the new and predicate tobacco products, the number of replicates, mean values, and standard deviation are needed for the menthol measurements.

2. Your SE Report does not provide target specifications and upper and lower range limits for all design parameters. The following additional information is required in order to adequately characterize the new and predicate tobacco products:

    a. Your SE Report provides target specifications and range limits for cigarette paper band diffusivity for the new and predicate tobacco products and cigarette paper band porosity for the predicate tobacco

products. Band porosity measures permeability which allows for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. Therefore, target specifications and upper and lower range limits for cigarette paper band porosity is needed for the new and predicate tobacco products. Or, a correlation between diffusivity and porosity is needed to allow for a scientific comparison of the two parameters.

b. Your SE Report does not include the upper and lower range limits for filter total denier and denier per filament in the new and predicate tobacco products.

For the parameters above, if a difference exists between the new and predicate tobacco products, scientific evidence is needed to demonstrate that the difference does not cause the new tobacco product to raise different questions of public health.

3. Your SE Report does not contain all of the necessary testing information to confirm the target specifications are met. In order to fully evaluate whether or not the target specifications are met, all of the following information is needed:

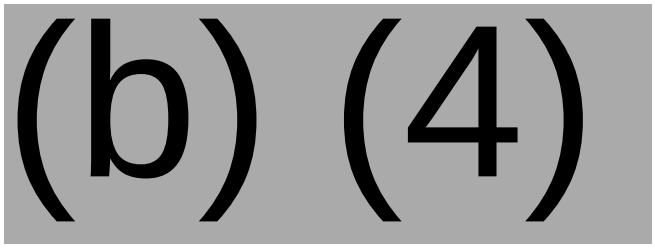
   a. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for filter density, filter total denier, filter denier per filament, plug wrap length, cigarette paper base paper basis weight, and cigarette paper base paper porosity for the new and predicate tobacco products.
   b. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for cigarette paper band porosity for the new and predicate tobacco products and the quantitative acceptance criteria for the cigarette paper band porosity of the new tobacco product.

   Certificates of analysis (COAs) from the material supplier may satisfy this deficiency if the COAs include a target specification, quantitative acceptance criteria, parameter units, test data average value, and either the standard deviation of the test data or the minimum and maximum values of the test data.

4. Your SE Report explains that the cigarette draw resistance target specifications are adjusted if the manufacturing data shows an increasing or decreasing trend. (b) (4) [redacted] Therefore, the target specification reported to the FDA was not consistent with the specification in place at the time of the

production data that was submitted. Target specifications should provide the exact manufacturing standard to which each design parameter must conform. Range limits should characterize a tobacco product based on the target specifications and desired product characteristics. Test data should demonstrate that a tobacco product conforms to the target specifications and range limits. When manufacturing data does not fall within the range limits of the specification, it is an indication that deviations are occurring (e.g., raw materials are out of specification, equipment malfunction). By changing the target specification on a continuous basis to meet the production data, the target specification is no longer representing the product characteristics. Therefore, a rationale for this process is needed to demonstrate that shifting the target specification for cigarette draw resistance has not created a difference in the product characteristics over time. If target specifications change, then product characteristics change, resulting in a new tobacco product that requires a marketing order under section 910 of the FD&C Act.

5. Your SE Report lists ingredients in the new tobacco product that are not present in the predicate tobacco products:



Your SE Report includes studies regarding the toxicity of these ingredients. However, the studies involve cigarettes that are not the new tobacco product which is subject of your SE Report. Furthermore, the cigarettes examined in the studies do not have the same or similar ingredients as the new tobacco product. Your SE Report cites the GRAS designation of these ingredients, but cigarettes are not food products and not intended for ingestion; the GRAS designation for food does not necessarily mean that the ingredients are safe for inhalation. Furthermore, your contention that addition of these ingredients does not significantly change HPHC yields cannot be confirmed because of the issues described in Deficiency 6. Therefore, scientific evidence and discussion is needed to explain how the addition of these ingredients does not cause the new tobacco product to raise different questions of public health.

6. Your SE Report indicates that the new tobacco product produces significantly higher yields of numerous HPHCs compared to the predicate tobacco product. Your SE Report provides a Quantitative Risk Assessment (QRA) which you claim demonstrates that the significant increases in HPHC yields in the new tobacco product do not raise different questions of public health.

However, the submitted QRA is not adequate to demonstrate substantial equivalence for the following reasons:

- The QRA is based on estimates of statistical variation that were derived from HPHC data from >100 cigarette brands and no evidence was provided to demonstrate that the data can be extrapolated to the new and predicate tobacco products.
- The QRA includes HPHC data that used the ISO smoking regimen for some HPHCs and the CI smoking regimen for other HPHCs, resulting in the summing of calculated risks based on different smoking regimens.
- The QRA did not use important inhalation dosimetry parameters such as those listed in the updated USEPA RAGS F guideline.

Therefore, scientific evidence and discussion is needed to explain how the significant increases in HPHC yields do not cause the new tobacco product to raise different questions of public health.

7. The most significant difference between the new and predicate tobacco products related to consumer perception and use is the placement of a capsule containing menthol in the filter of the new tobacco product. The new tobacco product's flavor delivery system allows users to choose whether to smoke the new tobacco product with or without menthol, effectively creating an adjustable menthol/non-menthol cigarette. In addition, non-menthol and menthol-smokers can share cigarette packs of the new tobacco product. As a result, this difference in flavor delivery system between the new and predicate tobacco products may influence consumer perception and use by providing users with a novel, versatile flavor delivery system. FDA requested you provide data to support your assertions that the change in flavor delivery system does not impact tobacco perception and use such that the new tobacco product does not raise different questions of public health. In response, you provided a summary of trend data from the (b) (4) However, the following issues prevent FDA from reaching the same conclusions as you:

   a. You did a (b) (4) trend analysis from the (b) (4) and stated that overall (b) (4) showed a statistically significant decline during the time period of the (b) (4). Therefore, in this trend analysis, you compared the (b) (4) associated with the new tobacco product against the (b) (4) (b) (4), arguing that introduction

of the new tobacco product to the (b) (4) did not detectably change (b) (4). However, determination of substantial equivalence is based on comparison of a new tobacco product to a predicate tobacco product, so your comparison of the new tobacco product to the (b) (4) (b) (4) is not appropriate. Furthermore, because the (b) (4)

b. You also provided (b) (4) comparing the new tobacco and predicate tobacco products and stated that the (b) (4) is not different between the two products. However, because there were (b) (4) of the new and predicate tobacco products in the (b) (4) the (b) (4) was not adequately powered to detect differences in (b) (4) between the new and predicate tobacco products. For example, when calculating (b) (4) (b) (4), you reported a (b) (4) (b) (4) for the new tobacco product (b) (4) (b) (4) for Kool Filter Kings. A meaningful comparison between products cannot be made because (b) (4) (b) (4) Because of the (b) (4) (b) (4), statistical analyses and estimates are likely unreliable.

8. Your SE Report includes a new tobacco product that has a different flavor than the predicate tobacco product due to the following differences between the products:

    - Sweeteners and other flavors quantities
    - Menthol yields

    Data that you submitted in your March 2015 amendment demonstrates an increase in menthol smoke yields by (b) (4) under the CI smoking regimen and (b) (4) under the ISO smoking regimen in the new tobacco product compared to the predicate tobacco product. Differences in sugars and flavors in cigarettes can mitigate their aversiveness and enhance product appeal. For example, adding flavors and sweeteners may increase the product's palatability, which influences abuse liability and may influence initiation behaviors, tobacco dependence, and continued use. The increase in menthol yield in the new product may increase the likelihood of initiation and progression to regular use, increase level/severity of dependence, and/or decrease likelihood of cessation success. You state that the (b) (4) results demonstrate that the difference in sugars and menthol level between Camel Crush Bold and Kool Filter Kings Box do not raise different questions of public health. However, as explained Deficiency 7, we have determined the (b) (4) data are not sufficient

to determine differences in use behaviors between the new and predicate tobacco products. Therefore, you did not provide adequate evidence that the differences in sweeteners and menthol levels between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. Specifically, you did not adequately address the (b) (4) and (b) (4) increase in menthol yields.

Following the deficiencies in the NSE order letter, the following text should be inserted:

In addition to these deficiencies, it should be noted that the tobacco blend in the new and predicate tobacco products was not fully characterized because you provided quantities as percentages and did not provide information in order to determine absolute quantities of each tobacco (in milligrams per cigarette). If you choose to submit a new SE Report for the new tobacco product in the future, you should provide tobacco quantities in absolute values.

6.2. DEFICIENCIES FOR SE0000277

The NSE order letter for SE0000277 should cite the following deficiencies:

1. Your SE Report does not provide target specifications and upper and lower range limits for all design parameters. The following additional information is required in order to adequately characterize the new and predicate tobacco products:

    a. Your SE Report provides target specifications and range limits for cigarette paper band diffusivity for the new and predicate tobacco products and cigarette paper band porosity for the predicate tobacco products. Band porosity measures permeability which allows for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. Therefore, target specifications and upper and lower range limits for cigarette paper band porosity is needed for the new and predicate tobacco products. Or, a correlation between diffusivity and porosity is needed to allow for a scientific comparison of the two parameters.
    b. Your SE Report does not include the upper and lower range limits for filter total denier and denier per filament in the new and predicate tobacco products.

    For the parameters above, if a difference exists between the new and predicate tobacco products, scientific evidence is needed to demonstrate that the difference does not cause the new tobacco product to raise different questions of public health.

2. Your SE Report does not contain all of the necessary testing information to confirm the target specifications are met. In order to fully evaluate whether or not the target specifications are met, all of the following information is needed:

    a. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for filter density, filter total denier, filter denier per filament, plug wrap length, cigarette paper base paper basis weight, and cigarette paper base paper porosity for the new and predicate tobacco products
    b. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for cigarette paper band porosity for the new and predicate tobacco products and the quantitative acceptance criteria for the cigarette paper band porosity of the new tobacco product

    Certificates of analysis (COAs) from the material supplier may satisfy this deficiency if the COAs include a target specification, quantitative acceptance criteria, parameter units, test data average value, and either the standard deviation of the test data or the minimum and maximum values of the test data.

3. Your SE Report provides the upper and lower range limits for filter pressure drop in the new tobacco product. Your SE Report explains that the filter rods are manufactured independently of the cigarettes and, in turn, may have different range limits compared to the individual filter segments that are subject to further manufacturing and incorporated into the cigarette. The supplier's COA pertains to the filter rod, not the filter segment. However, your SE Report explains that, as a result of the variability when the rod is cut, your range limits are slightly wider than the supplier's range limits. It is unclear how the filter segment lengths vary when the cutting process is precise to (b) (4) Furthermore, if the filter length ranges are tight, the filter pressure drop ranges should mimic closely. Typically, the filter segment pressure drop is very similar, if not equal, to the filter rod pressure drop when divided by the cut number. You have not justified how the segment length difference translates into the pressure drop difference apparent between your range limits and the supplier's range limits.

4. Your SE Report indicates that the new tobacco product produces significantly higher yields of numerous HPHCs compared to the predicate tobacco product. Your SE Report provides a Quantitative Risk Assessment (QRA) which you claim demonstrates that the significant increases in HPHC yields in the new tobacco product do not raise different questions of public health. However, the submitted QRA is not adequate to demonstrate substantial equivalence for the following reasons:

    - The QRA is based on estimates of statistical variation that were derived from HPHC data from >100 cigarette brands and no evidence was provided to demonstrate that the data can be extrapolated to the new and predicate tobacco products.
    - The QRA includes HPHC data that used the ISO smoking regimen for some HPHCs and the CI smoking regimen for other HPHCs, resulting in the summing of calculated risks based on different smoking regimens.
    - The QRA did not use important inhalation dosimetry parameters such as those listed in the updated USEPA RAGS F guideline.

    Therefore, scientific evidence and discussion is needed to explain how the significant increases in HPHC yields do not cause the new tobacco product to raise different questions of public health.

Following the deficiencies in the NSE order letter, the following text should be inserted:

> In addition to these deficiencies, it should be noted that the tobacco blend in the new and predicate tobacco products was not fully characterized because you provided quantities as percentages and did not provide information in order to determine absolute quantities of each tobacco (in milligrams per cigarette). If you choose to submit a new SE Report for the new tobacco product in the future, you should provide tobacco quantities in absolute values.

6.3. DEFICIENCIES FOR SE0000278

The NSE order letter for SE0000278 should cite the following deficiencies:

1. Your April 2015 amendment indicates that the tobacco blend for the new tobacco product was changed on (b) (4) It is unclear whether HPHC data provided in your SE Report was for the new tobacco product that is the subject of SE0000278 (the product with the tobacco blend prior to (b) (4) or the product with the tobacco blend on or after (b) (4)

2. Your SE Report does not provide target specifications and upper and lower range limits for all design parameters. The following additional information is

required in order to adequately characterize the new and predicate tobacco products:

a. Your SE Report provides target specifications and range limits for cigarette paper band diffusivity for the new and predicate tobacco products and cigarette paper band porosity for the predicate tobacco products. Band porosity measures permeability which allows for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. Therefore, target specifications and upper and lower range limits for cigarette paper band porosity is needed for the new and predicate tobacco products. Or, a correlation between diffusivity and porosity is needed to allow for a scientific comparison of the two parameters.
b. Your SE Report does not include the upper and lower range limits for filter total denier and denier per filament in the new and predicate tobacco products.

For the parameters above, if a difference exists between the new and predicate tobacco products, scientific evidence is needed to demonstrate that the difference does not cause the new tobacco product to raise different questions of public health.

3. Your SE Report does not contain all of the necessary testing information to confirm the target specifications are met. In order to fully evaluate whether or not the target specifications are met, all of the following information is needed:

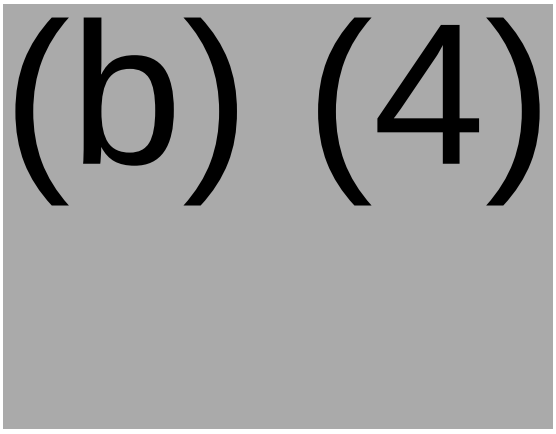
a. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for filter density, filter total denier, filter denier per filament, plug wrap length, cigarette paper base paper basis weight, and cigarette paper base paper porosity for the new and predicate tobacco products
b. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for cigarette paper band porosity for the new and predicate tobacco products and the quantitative acceptance criteria for the cigarette paper band porosity of the new tobacco product

Certificates of analysis (COAs) from the material supplier may satisfy this deficiency if the COAs include a target specification, quantitative acceptance criteria, parameter units, test data average value, and either the standard deviation of the test data or the minimum and maximum values of the test data.

4. Your SE Report provides the upper and lower range limits for filter pressure drop in the new tobacco product. Your SE Report explains that the filter rods are manufactured independently of the cigarettes and, in turn, may have

different range limits compared to the individual filter segments that are subject to further manufacturing and incorporated into the cigarette. The supplier's COA pertains to the filter rod, not the filter segment. However, your SE Report explains that, as a result of the variability when the rod is cut, your range limits are slightly wider than the supplier's range limits. It is unclear how the filter segment lengths vary when the cutting process is precise to (b) (4) Furthermore, if the filter length ranges are tight, the filter pressure drop ranges should mimic closely. Typically, the filter segment pressure drop is very similar, if not equal, to the filter rod pressure drop when divided by the cut number. You have not justified how the segment length difference translates into the pressure drop difference apparent between your range limits and the supplier's range limits.

5. Your SE Report lists ingredients in the new tobacco product that are not present in the predicate tobacco products:



Your SE Report includes studies regarding the toxicity of these ingredients. However, the studies involve cigarettes that are not the new tobacco product which is subject of your SE Report. Furthermore, the cigarettes examined in the studies do not have the same or similar ingredients as the new tobacco product. Your SE Report cites the GRAS designation of these ingredients, but cigarettes are not food products and not intended for ingestion; the GRAS designation for food does not necessarily mean that the ingredients are safe for inhalation. Furthermore, your contention that addition of these ingredients does not significantly change HPHC yields cannot be confirmed because of the issues described in Deficiency 6. Therefore, scientific evidence and discussion is needed to explain how the addition of these ingredients does not cause the new tobacco product to raise different questions of public health.

6. Your SE Report indicates that the new tobacco product produces significantly higher yields of numerous HPHCs compared to the predicate tobacco product. Your SE Report provides a Quantitative Risk Assessment (QRA) which you claim demonstrates that the significant increases in HPHC yields in the new tobacco product do not raise different questions of public health.

However, the submitted QRA is not adequate to demonstrate substantial equivalence for the following reasons:

- The QRA is based on estimates of statistical variation that were derived from HPHC data from >100 cigarette brands and no evidence was provided to demonstrate that the data can be extrapolated to the new and predicate tobacco products.
- The QRA includes HPHC data that used the ISO smoking regimen for some HPHCs and the CI smoking regimen for other HPHCs, resulting in the summing of calculated risks based on different smoking regimens.
- The QRA did not use important inhalation dosimetry parameters such as those listed in the updated USEPA RAGS F guideline.
- The QRA includes HPHC data generated from the new tobacco product containing the tobacco blend used (b) (4) and this blend is not the blend included in the new tobacco product on the date that the SE Report was submitted.

Therefore, scientific evidence and discussion is needed to explain how the significant increases in HPHC yields do not cause the new tobacco product to raise different questions of public health.

7. Your SE Report indicates that the new tobacco product has different flavors than the predicate tobacco product due to differences in sweeteners and other flavors. Your April 2015 amendment states that the (b) (4) results demonstrate that there are no differences between the new and predicate tobacco products. Data from the (b) (4) (b) (4) during the (b) (4) period of assessments for the new tobacco product does not include (b) (4) (b) (4) . In addition, there was no information provided specifically about use of the predicate products; the new tobacco products were compared to (b) (4) . (b) (4) (b) (4) and information about the predicate tobacco product was not provided, there are insufficient data to compare the new and predicate tobacco products using the (b) (4)(b) (4) Therefore, there is not adequate evidence to demonstrate that the differences in flavors between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

Following the deficiencies in the NSE order letter, the following text should be inserted:

In addition to these deficiencies, it should be noted that the tobacco blend in the new and predicate tobacco products was not fully characterized because you provided quantities as percentages and did not provide information in order to determine absolute quantities of each tobacco (in milligrams per cigarette). If you choose to submit a new SE Report for the new tobacco

product in the future, you should provide tobacco quantities in absolute values.

6.4. DEFICIENCIES FOR SE0000281

The NSE order letter for SE0000281 should cite the following deficiencies:

1. Your April 2015 amendment indicates that the tobacco blend for the new tobacco product was changed on (b) (4) It is unclear whether HPHC data provided in your SE Report was for the new tobacco product that is the subject of SE0000281 (the product with the tobacco blend prior to (b) (4) or the product with the tobacco blend on or after (b) (4)

2. Your SE Report does not provide target specifications and upper and lower range limits for all design parameters. The following additional information is required in order to adequately characterize the new and predicate tobacco products:

    a. Your SE Report provides target specifications and range limits for cigarette paper band diffusivity for the new and predicate tobacco products and cigarette paper band porosity for the predicate tobacco products. Band porosity measures permeability which allows for the overall assessment of the change or weighted change in air flow through the cigarette paper during active puffing. Therefore, target specifications and upper and lower range limits for cigarette paper band porosity is needed for the new and predicate tobacco products. Or, a correlation between diffusivity and porosity is needed to allow for a scientific comparison of the two parameters.
    b. Your SE Report does not include the upper and lower range limits for filter total denier and denier per filament in the new and predicate tobacco products.

    For the parameters above, if a difference exists between the new and predicate tobacco products, scientific evidence is needed to demonstrate that the difference does not cause the new tobacco product to raise different questions of public health.

3. Your SE Report does not contain all of the necessary testing information to confirm the target specifications are met. In order to fully evaluate whether or not the target specifications are met, all of the following information is needed:

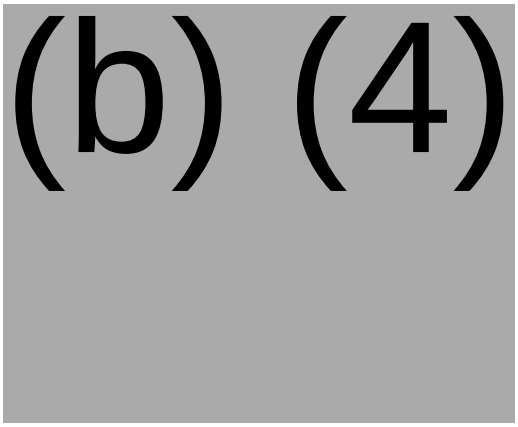
    a. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for filter density, filter total denier, filter denier per filament, plug wrap length, cigarette paper base paper basis weight, and cigarette paper base paper porosity for the new and predicate tobacco products

b. Full test data (including test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for cigarette paper band porosity for the new and predicate tobacco products and the quantitative acceptance criteria for the cigarette paper band porosity of the new tobacco product

Certificates of analysis (COAs) from the material supplier may satisfy this deficiency if the COAs include a target specification, quantitative acceptance criteria, parameter units, test data average value, and either the standard deviation of the test data or the minimum and maximum values of the test data.

4. Your SE Report provides the upper and lower range limits for filter pressure drop in the new tobacco product. Your SE Report explains that the filter rods are manufactured independently of the cigarettes and, in turn, may have different range limits compared to the individual filter segments that are subject to further manufacturing and incorporated into the cigarette. The supplier's COA pertains to the filter rod, not the filter segment. However, your SE Report explains that, as a result of the variability when the rod is cut, your range limits are slightly wider than the supplier's range limits. It is unclear how the filter segment lengths vary when the cutting process is precise to (b) (4). Furthermore, if the filter length ranges are tight, the filter pressure drop ranges should mimic closely. Typically, the filter segment pressure drop is very similar, if not equal, to the filter rod pressure drop when divided by the cut number. You have not justified how the segment length difference translates into the pressure drop difference apparent between your range limits and the supplier's range limits.

5. Your SE Report lists ingredients in the new tobacco product that are not present in the predicate tobacco products:



Your SE Report includes studies regarding the toxicity of these ingredients. However, the studies involve cigarettes that are not the new tobacco product which is subject of your SE Report. Furthermore, the cigarettes examined in the studies do not have the same or similar ingredients as the new tobacco

product. Your SE Report cites the GRAS designation of these ingredients, but cigarettes are not food products and not intended for ingestion; the GRAS designation for food does not necessarily mean that the ingredients are safe for inhalation. Furthermore, your contention that addition of these ingredients does not significantly change HPHC yields cannot be confirmed because of the issues described in Deficiency 6. Therefore, scientific evidence and discussion is needed to explain how the addition of these ingredients does not cause the new tobacco product to raise different questions of public health.

6. Your SE Report indicates that the new tobacco product produces significantly higher yields of numerous HPHCs compared to the predicate tobacco product. Your SE Report provides a Quantitative Risk Assessment (QRA) which you claim demonstrates that the significant increases in HPHC yields in the new tobacco product do not raise different questions of public health. However, the submitted QRA is not adequate to demonstrate substantial equivalence for the following reasons:

    - The QRA is based on estimates of statistical variation that were derived from HPHC data from >100 cigarette brands and no evidence was provided to demonstrate that the data can be extrapolated to the new and predicate tobacco products.
    - The QRA includes HPHC data that used the ISO smoking regimen for some HPHCs and the CI smoking regimen for other HPHCs, resulting in the summing of calculated risks based on different smoking regimens.
    - The QRA did not use important inhalation dosimetry parameters such as those listed in the updated USEPA RAGS F guideline.
    - The QRA includes HPHC data generated from the new tobacco product containing the tobacco blend used (b) (4) and this blend is not the blend included in the new tobacco product on the date that the SE Report was submitted.

    Therefore, scientific evidence and discussion is needed to explain how the significant increases in HPHC yields do not cause the new tobacco product to raise different questions of public health.

7. Your SE Report indicates that the new tobacco product has different flavors than the predicate tobacco product due to differences in sweeteners and other flavors. Your April 2015 amendment states that the (b) (4) results demonstrate that there are no differences between the new and predicate tobacco products. Data from the (b) (4) (b) (4) during the (b) (4) period of assessments for the new tobacco product (b) (4) (b) (4). In addition, there was no information provided specifically about use of the predicate products; (b) (4) (b) (4)

(b) (4) (b) (4) and information about the predicate tobacco product was not provided, there are insufficient data to compare the new and predicate tobacco products using the (b) (4) (b) (4)y. Therefore, there is not adequate evidence to demonstrate that the differences in flavors between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

Following the deficiencies in the NSE order letter, the following text should be inserted:

In addition to these deficiencies, it should be noted that the tobacco blend in the new and predicate tobacco products was not fully characterized because you provided quantities as percentages and did not provide information in order to determine absolute quantities of each tobacco (in milligrams per cigarette). If you choose to submit a new SE Report for the new tobacco product in the future, you should provide tobacco quantities in absolute values.