DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
10903 New Hampshire Avenue
Silver Spring, MD 20993

September 15, 2015

NOT SUBSTANTIALLY EQUIVALENT

R.J. Reynolds Tobacco Company
Attention: James E. Swauger, Ph.D., DABT
Vice President, Regulatory Oversight, RAI Services Company
401 N. Main Street, P.O. Box 2959
Winston-Salem, N.C. 27101

FDA Submission Tracking Number (STN): SE0000276

Dear Dr. Swauger:

We have completed our review of your Report Preceding Introduction of Certain Substantially Equivalent Products into Interstate Commerce (SE Report), submitted under section 905(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for the following tobacco product:

New Tobacco Product

Tobacco Product Manufacturer:	R.J. Reynolds Tobacco Company
Tobacco Product Name[1]:	Camel Crush Bold
Tobacco Product Category:	Cigarette
Tobacco Product Sub-Category	Filtered, Combusted
Package Type:	Box
Package Quantity:	20 cigarettes
Characterizing Flavor:	Menthol
Length:	83 mm
Diameter:	7.8 mm
Filter Ventilation:	20%
Additional Property:	Crushable menthol capsule in filter

[1] Brand/sub-brand or other commercial name used in commercial distribution

We have completed the review of your SE Report and have determined that it does not establish that the new tobacco product specified is substantially equivalent to the following predicate tobacco product:

Predicate Tobacco Product

Tobacco Product Manufacturer:	R.J. Reynolds Tobacco Company
Tobacco Product Name[2]:	Kool Filter Kings Box
Tobacco Product Category:	Cigarette
Tobacco Product Sub-Category:	Filtered, Combusted
Package Type:	Box
Package Quantity:	20 cigarettes
Characterizing Flavor:	Menthol
Length:	83 mm
Diameter:	7.8 mm
Filter Ventilation:	20%
Additional Property:	None

We have described below our basis for this determination.

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.

[2] Brand/sub-brand or other commercial name used in commercial distribution

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) 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:

(b) (4)

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) [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) associated with the new tobacco product

against the (b) (4), arguing that introduction of the new tobacco product to the (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 that (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 Kool Filter Kings. A meaningful comparison between products cannot be made because of the (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) (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)(b) (4) and (b) (4) increase in menthol yields.

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.

You have failed to provide sufficient information to support a finding of substantial equivalence; therefore, we are issuing an order finding that this new tobacco product is not substantially equivalent to an appropriate predicate tobacco product. Upon issuance of this order, your tobacco product is misbranded under section 903(a)(6) of the FD&C Act and adulterated under section 902(6)(A) of the FD&C Act. Therefore, you must immediately stop all distribution, importation, sale, marketing, and promotion of your tobacco product in the United States. Failure to comply with the FD&C Act may result in FDA taking regulatory action without further notice. These actions may include, but are not limited to, civil money penalties, seizure, and/or injunction.

Additionally, FDA requests that within 15 days of this letter you submit a plan detailing the steps you plan to take to ensure that this misbranded and adulterated product is not further distributed, imported, sold, marketed, or promoted in the United States by others. Your plan should include information sufficient to distinguish this misbranded and adulterated product from legally marketed tobacco products, including, but not limited to lot numbers, manufacturing codes, and manufacturing dates. The plan should also include a list of your direct accounts, and contain their contact information. Submit your plan to the address below with a cover letter that includes the following text in the subject line:

COMPLIANCE PLAN for SE0000276

FDA will post product identifying information on a list of tobacco products that are adulterated and misbranded due to an NSE order, available to the public at http://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm339928.htm

We remind you that you are required to update your listing information in June and December of each year under section 905(i)(3) of the FD&C Act. As part of this listing update, under section 905(i)(3)(B) of the FD&C Act, you must provide information on the date of discontinuance and product identity for any product you discontinue.

If you wish to request supervisory review of this decision under 21 CFR 10.75, please submit the request via the FDA Electronic Submission Gateway (www.fda.gov/esg) using eSubmitter, or mail to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We request that your package be sent as a single submission with a cover letter that includes the following text in your subject line: **REQUEST FOR SUPERVISORY REVIEW for SE0000276.** In addition, we request that your package identify each basis for the request and contain all information on which you wish your request to be based; it may not contain any new data or analysis that was not part of your SE Report.

You may not legally market the new tobacco product described in this SE Report unless (1) FDA issues an order finding the product to be exempt from the requirements of substantial equivalence and you make the required submission under section 905(j)(1)(A)(ii) of the FD&C Act, (2) FDA issues an order finding the product substantially equivalent to a predicate tobacco product (section 910(a)(2)(A) of the FD&C Act), OR (3) FDA issues an order authorizing introduction or delivery for introduction into interstate commerce under a premarket tobacco application (section 910(c)(1)(A) of the FD&C Act).

See the following website for additional information on these three pathways: http://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/NewTobacco ProductReviewandEvaluation/default.htm.

If you have any questions, please contact Kim Collins, Lead Regulatory Health Project Manager, at (301) 796-1556.

Sincerely,

Digitally signed by David Ashley -S
Date: 2015.09.15 06:44:05 -04'00'

David L. Ashley, Ph.D.
RADM, United States Public Health Service
Director, Office of Science
Center for Tobacco Products