U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

July 31, 2018

NOT SUBSTANTIALLY EQUIVALENT

ITG Brands, LLC
Attention: Carole Folmar, Director of Regulatory & Scientific Affairs
714 Green Valley Road
Greensboro, NC 27408

FDA Submission Tracking Number (STN): SE0006260

Dear Ms. Folmar:

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

Date of Submission:	March 22, 2011
Date of Receipt:	March 22, 2011
Product Manufacturer:	ITG Brands, LLC
Product Name:[1]	Salem Slim 100's Box
Product Category:	Cigarettes
Product Sub-Category:	Combusted, Filtered
Package Type:	Box
Package Quantity:	20 per pack
Characterizing Flavor:	Menthol
Length:	99 mm
Diameter:[2]	7.4 mm
Ventilation:	47%

[1] Brand/sub-brand or other commercial name used in commercial distribution
[2] The applicant submitted the circumference which allowed for a calculation of diameter

We have determined that your SE Report does not establish that the new tobacco product specified above is substantially equivalent to the following predicate tobacco product:

Predicate Tobacco Product

Product Manufacturer:	ITG Brands, LLC
Product Name:[3]	Salem Lights Green Label Box
Product Category:	Cigarettes
Product Sub-Category:	Combusted, Filtered
Package Type:	Box
Package Quantity:	20 per pack
Characterizing Flavor:	Menthol
Length:	98 mm
Diameter:[4]	7.2 mm
Ventilation:	47%

We have described below our basis for this determination.

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

2. Your SE Report states that the new product has higher amounts or different ingredients in the new product compared to the remanufactured predicate product which is used in lieu of the predicate product. Specifically, (b) (4) in the tobacco, are 55%, 44%, 68%, and 1,240% higher, respectively, than the remanufactured predicate product. Additionally, (b) (4) was added along with other ingredients to the cigarette paper, tipping paper adhesive, filter center line adhesive, and tipping paper.

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

[3] Brand/sub-brand or other commercial name used in commercial distribution
[4] The applicant submitted the circumference which allowed for a calculation of diameter

appeal. You needed to provide scientific evidence and rationale as to why the differences in the ingredients between the new and predicate products does not cause the new product to raise different questions of public health.

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

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

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

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

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

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

questions of public health:

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

5. Your SE Reports contain side-by-side comparisons of all of the necessary design parameter target specifications and upper and lower range limits for the predicate product and corresponding remanufactured predicate product. However, for the new and predicate tobacco products, your December 2017 amendment includes inconsistencies in the target specifications of several design parameters from those provided in your previous amendments. You state that the target specifications have been updated since the previous amendments and indicate that differences in the values are due to reporting errors that you have noted or to the rounding to different significant figures between amendments. However, for the new and predicate tobacco products, the differences in the target specifications among your amendments is too large to be due to differences in significant figures. Furthermore, the parameter values have changed across multiple amendments, which limits the possibility of the error being due to reporting mistakes. If you choose to use remanufactured predicate products to extrapolate test data to the corresponding predicate products as you have done, then the predicate product and remanufactured predicate product needs to be fully characterized to determine whether the remanufactured predicate product test data can be extrapolated to the predicate product.

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

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

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

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

Upper and lower range limits

a. Tobacco rod density (predicate product)
b. Cigarette paper base paper porosity (new and predicate products)
c. Filter total denier (new and predicate products)
d. Filter ventilation (new product)

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

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

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

COAs cannot be used to confirm whether the specifications for cigarette paper band porosity have been met for the new product. You needed to provide complete COAs for cigarette paper band porosity for the new and predicate products.

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

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

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

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

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

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

    b. A detailed explanation of any route-to-route extrapolations, including input data, assumptions, equations and outputs.

    c. A detailed selection criteria for the selection of reference values and scientific evidence for deviating from established reference values. Include additional evidence or rationale for selected reference values, given the availability of multiple reference values for a specific constituent. Any rationale should include scientific evidence for deviating in methodology from the National Research Council and the Guidelines for Carcinogen Risk Assessment.

    d. Evidence that the reference values used in the calculation of the HQ or ILCR, and used in both the QRA and PRA, are appropriate for the toxicological endpoints associated with the use of the new and predicate products.

    e. A clear description of how you intend to characterize and interpret the QRA and PRA results. In the 'Problem Formulation' section, you state that "*the risk assessment (i.e., QRA) presented herein does not concern absolute risk or hazard but rather the comparative risk or hazard between the two products (i.e., Subject and Reman*

Predicate/Predicate)." However, you provided data and a discussion relating to the absolute risk or hazard (e.g., the total cancer risk or margin-of-exposure).

f. Specific evidence or rationale for the inclusion of body weight and daily inhalation rate in your estimation of exposure concentrations regarding the smoker exposure scenario.

g. Clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime is appropriate for the specific products and user populations.

h. All raw data, equations, assumptions, parameters, outputs, and references used in the QRA and PRA, including the HPHC data, methods used to determine statistical variability and any other pertinent data used in these calculations.

i. A complete description of the PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. For example, although the assumed minimum, maximum and "likeliest" values for the distributions are provided, no justifications for the use of Beta PERT distributions (used for Cigarettes per Day (CpD), Exposure Duration (ED), Averaging Time (AT)) or Gamma distribution (used for Daily Inhalation Rate (DIR)) are given. Provide scientific evidence that the parameter ranges and means are specific to the new and predicate products and the expected user populations. Consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions.

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

k. Evidence that the daily inhalation parameter used in the reference you cited, Marano et al, 2012, 193.99 L/kg-d, is appropriate for tobacco product-specific

exposures as well as the population expected to use the new and predicate products.

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

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

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. 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 SE0006260

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 https://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/ucm371765.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 CTP Portal (http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/uc

m515047.htm)[5] using eSubmitter (http://www.fda.gov/ForIndustry/FDAeSubmitter), or mail it to:

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

The CTP Portal and FDA Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; if the upload is successful, submissions are considered received by DCC on the day of upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date (see http://www.fda.gov/tobaccoproducts/aboutctp/contactus/default.htm); if the due date falls on a weekend or holiday the delivery must be received on or before the preceding business day. We are unable to accept regulatory submissions by e-mail.

We ask that your request be sent as a single submission with a cover letter that includes the following text in your subject line: **REQUEST FOR SUPERVISORY REVIEW for SE0006260**. In addition, we ask you to identify each basis for the request and include 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.

In order to legally market the new product described in this application, it must comply with the requirements in section 910(a)(2)(A) of the FD&C Act.

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

If you have any questions, please contact Megan Nguyen, Regulatory Health Project Manager, at (301) 796 - 7826 or Megan.Nguyen@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2018.07.31 11:11:12 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

[5] The FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.