Technical Project Lead (TPL) Review:
SE Reports SE0000282 – SE0000288

SE0000282: Ariva Cinnamon	
Length	10.4 mm
Width	6.65 mm
Thickness	5.79 mm
Portion Size	Not provided
Package Quantity	10 tablets
Package Type	Carton with a 10-count blister pack
SE0000283: Ariva Wintergreen	
Length	10.4 mm
Width	6.65 mm
Thickness	5.79 mm
Portion Size	Not provided
Package Quantity	10 tablets
Package Type	Carton with a 10-count blister pack
SE0000284: Ariva Mint	
Length	10.4 mm
Width	6.65 mm
Thickness	5.79 mm
Portion Size	Not provided
Package Quantity	10 tablets
Package Type	Carton with a 10-count blister pack
SE0000285: Ariva Java	
Length	10.4 mm
Width	6.65 mm
Thickness	5.79 mm
Portion Size	Not provided
Package Quantity	10 tablets
Package Type	Carton with a 10-count blister pack
SE0000286: Stonewall Natural	
Length	14.0 mm
Width	8.99 mm
Thickness	5.66 mm
Portion Size	Not provided
Package Quantity	20 tablets
Package Type	Carton with two 10-count blister packs

SE0000287: Ariva Citrus	
Length	10.4 mm
Width	6.65 mm
Thickness	5.79 mm
Portion Size	Not provided
Package Quantity	10 tablets
Package Type	Carton with a 10-count blister pack
SE0000288: Stonewall Java	
Length	14.0 mm
Width	8.99 mm
Thickness	5.66 mm
Portion Size	Not provided
Package Quantity	20 tablets
Package Type	Carton with two 10-count blister packs
Common Attributes of SE Reports	
Applicant	Star Scientific, Inc.
Status	Provisional
Product Category	Smokeless Tobacco Product
Product Sub-Category	Dissolvable (Tablets)
Recommendation	
Issue Not Substantially Equivalent (NSE) orders	

Technical Project Lead (TPL):

Signature:

Digitally signed by Matthew R. Holman -S
Date: 2014.08.27 10:07:15 -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: 2014.08.27 11:44:31 -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 information for the predicate tobacco products:

Table 1. Predicate Products

Original Ariva (SE0000282, SE0000283, SE0000284, SE0000285, SE0000287)	
Length	10.4 mm
Width	6.65 mm
Thickness	5.66 mm
Portion Size	Not provided
Package Quantity	20 tablets
Package Type	Carton with two 10-count blister packs
Original Stonewall (SE0000286, SE0000288)	
Length	14.0 mm
Width	8.99 mm
Thickness	5.66 mm
Portion Size	Not provided
Package Quantity	20 tablets
Package Type	Carton with two 10-count blister packs

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

The applicant submitted the seven SE Reports on March 18, 2011. FDA sent the applicant administrative Advice/Information Request letters (A/I letters) for these SE Reports in November 2012. In response to the administrative A/I letters, the applicant amended its SE Reports in December 2012. FDA sent a scientific A/I letter to the applicant in March 2014. The applicant did not amend its SE Reports in response to the scientific A/I letter. FDA sent a Preliminary Finding letter to the applicant on June 13, 2014 based on a memorandum by Alexis Morgan on that same date. A response to the Preliminary Finding letter was due from the applicant in July 2014. As of the date of this review, we have not received a response to that letter[1].

1.3. SCOPE OF REVIEW

This review captures all administrative and compliance reviews completed for SE0000282 – SE0000288.

[1] FDA has proof of delivery of the preliminary finding letter.

1.4. KEY DIFFERENCES BETWEEN NEW AND PREDICATE TOBACCO PRODUCTS

The key differences between the new and corresponding predicate tobacco products are as follows:

- Change in the (b) (4) (all SE Reports)
- Changes in (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287 only)
- (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287 only)
- (b) (4) (SE0000282, SE0000283, SE0000286, SE0000287, and SE0000288 only)
- (b) (4) (SE0000283, SE0000284, SE0000285, and SE0000287 only)
- (b) (4) (SE0000286 only)
- (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, SE0000287, and SE0000288 only)
- (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, SE0000287, and SE0000288 only)

It is possible that there are other key differences between the new and predicate products that we were not able to identify because the applicant did not provide information outlined in the scientific A/I and Preliminary Finding letters.

2. ADMINISTRATIVE REVIEW

Administrative completeness reviews were completed by Idara Udoh on November 8, 2012 and March 26, 2013. The memorandum by Alexis Morgan on June 13, 2014 also addresses administrative completeness.

The memorandum by Alexis Morgan concluded that the SE Reports were administratively incomplete because there was no side-by-side quantitative comparison with respect to “other features” of the tobacco products. However, the scientific reviews addressed the “other features,” so 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 are grandfathered products (i.e., were commercially marketed as of February 15, 2007). The OCE reviews dated May 17, 2013 and May 21, 2013, conclude that sufficient evidence was submitted by the applicant to demonstrate that the predicate tobacco products are eligible predicate tobacco products.

4. SCIENTIFIC REVIEW

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

4.1. CHEMISTRY

A chemistry review was completed by Shixia Feng, Ph.D. on August 22, 2013.

The chemistry review concludes that all new products when compared to their predicate products have different characteristics, but the information submitted failed to demonstrate that the new products do not raise different questions of public health. Therefore, in the scientific A/I letter and Preliminary Finding letter, the following information was required:

1. All of your SE Reports lack full characterization of all ingredients in all components and subcomponents. For example, in "section 3.1 Table 2 Listing of Ingredients for Original Ariva" of SE0000282, "(b) (4) is listed under the (b) (4) It is not clear what (b) (4) or (b) (4) means. It would be helpful to know the grade/purity and supplier of each ingredient. Provide detailed information of the ingredients in all components and subcomponents of the predicate and new products.

2. All of your SE Reports provide the measured pH values for the new products. However, the SE Reports do not provide pH values for the predicate products. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. Provide the measured pH values or the free nicotine levels based on measured pH values for the predicate products to support a finding of substantial equivalence between the new and predicate products. If the measured pH values or free nicotine levels based on measured pH values are significantly different than those for the new products, provide a scientific evidence and rationale as to why the differences do not cause the new product to raise different questions of public health.

3. In SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287, you indicate that there are many changes in ingredients in terms of quantity or type or both. The new products include (b) (4) (b) (4) than the predicate product. Additionally, the new products include a (b) (4) These differences may affect the release rates of the tobacco constituents. Provide adequate evidence and scientific rationale that

these differences do not cause the new products to raise different questions of public health. For example, constituent (e.g., nicotine) release data in artificial saliva (e.g., in vitro dissolution experiments) may provide such evidence.

4. All of your SE Reports provide average HPHC quantities, standard deviations, and 95% confidence limits for the new products. However, your SE Reports only provide average HPHC quantities for the predicate products. We cannot determine whether the differences in HPHCs between the new and corresponding predicate products are significant with only the average values. Provide full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) for all testing performed.

5. All of your SE Reports provide two separate sets of nicotine data in (b) (4) and (b) (4) reports. (b) (4) Provide an explanation for the discrepancies between the two measurements. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. Clarify which nicotine data set you intend to use for the determination of substantial equivalence. If you intend to use data from the (b) (4) report, provide data in mass per unit of product and detailed testing information (same information as indicated in deficiency #6 above) for both the predicate and new products.

6. In SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287, you provide numerical TSNA data for the new products. However, the SE Reports state that the (b) (4) and the TSNAs levels were reported as "NQ" for the predicate product. Therefore, we cannot determine the difference between the new and predicate products for these SE Reports. Several other HPHCs are presented as "NQ" and "BDL" (below the detection limit) as well. Provide complete information about the methodologies used to generate the HPHCs data including the limit of detection and limit of quantitation, accuracy and precision of the methods.

7. All of your SE Reports lack information about stability for the predicate and new products. Additional information about stability testing is needed to fully characterize the predicate and new products. Provide detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed. Provide a description of how the shelf life is indicated on the product. If the stability is identical for the predicate and new products, provide the

information for the new product and a statement that this information is identical for the predicate product. Additionally, provide any known or expected impacts of the differences in characteristics on the product stability. If no impact is known or expected, state as such.

8. All of your SE Reports lack information about complex ingredients. For example, in SE0000282, (b) (4) under the "Single Chemical CAS number/Complex Purchased Ingredients Information" in Table 3. Distinguish between complex ingredients made to your specifications and those that are not. For all complex ingredients made to your specifications, provide complete information according to FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

At this time, the applicant has not responded to the scientific A/I letter or Preliminary Finding letter. Therefore, the applicant has not demonstrated that the new tobacco products do not raise different questions of public health from a chemistry perspective.

4.2. ENGINEERING

An engineering review was completed by Christian Coyle, Ph.D. on August 22, 2013.

The engineering review concludes that all new products when compared to their predicate products have different characteristics, but the information submitted failed to demonstrate that the new products do not raise different questions of public health. Therefore, in the scientific A/I letter and Preliminary Finding letter, the following information was required:

9. All of your SE Reports provide limited information on the design parameters for the predicate and new products. However, your SE Reports do not include all of the design parameters required to fully characterize the predicate and new products. In order to adequately characterize the products, it is necessary to compare key design parameters. Provide the **target specification and upper and lower range limits** for the following smokeless tobacco design parameter for each predicate and new product:

    a. Tobacco particle size (mm)

    Provide the **target specification** for the following smokeless tobacco design parameter for each predicate and new product:

    b. Portion weight (mg)

Provide the **upper and lower range limits** for the following smokeless tobacco design parameters for each predicate and new product:

c. Final tobacco moisture (%);
d. Portion length (mm);
e. Portion width (mm); and
f. Portion thickness (mm)

For each of the above parameters, provide the requested data per one unit of product (e.g., portion length should be reported in mm per portion). If a difference exists between the new and corresponding predicate products, provide a rationale for each modification of the target specification and range limits with evidence and a scientific discussion of why the change does not cause the new product to raise different questions of public health.

10. All of your SE Reports include design parameter specifications but do not include raw data confirming that specifications are met. Provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the results for all testing performed for the following smokeless tobacco design parameters for each predicate product:

    a. Tobacco particle size (mm);
    b. Final tobacco moisture (%); and
    c. Portion weight (mg).

    Certificates of analysis from the material supplier may satisfy this deficiency. Additionally, for all of the design parameters that were tested according to national or international standards, identify the standards and state what deviations, if any, from the standards occurred.

At this time, the applicant has not responded to the scientific A/I letter or Preliminary Finding letter. Therefore, the applicant has not demonstrated that the new tobacco products do not raise different questions of public health from an engineering perspective.

4.3. TOXICOLOGY

A toxicology review was completed by Mamata De, Ph.D. on January 23, 2014.

The toxicology review concludes that all new products when compared to their predicate products have different characteristics, but the information submitted failed to demonstrate that the new products do not raise different questions of public health. Therefore, in the scientific A/I letter and Preliminary Finding letter, the following information was required:

11. In SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287, there were substantial increases in several chemicals, specifically (b) (4) and metals such as (b) (4) which are on the FDA HPHC list. These chemicals are known to have carcinogenic, cardiovascular, or sensitization properties. Address why the increases in these chemicals do not cause the new products to raise different questions of public health.

12. In SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287, the levels of carcinogenic compounds such as acetaldehyde, NNN, and NNK were reported for the new product but not compared with their corresponding predicate product. These chemicals are known to be carcinogenic. Provide the levels found in the predicate products and information to show that any differences in the levels of acetaldehyde, NNN, and NNK do not cause the new products to raise different questions of public health.

13. In SE0000288, there were substantial increases in several chemicals, specifically (b) (4), and metals such as (b) (4), all of which are on the FDA HPHC list. Address why the increases in these chemicals do not cause the new product to raise different questions of public health.

14. In SE0000286, there were substantial increases in (b) (4), which is on the FDA HPHC list. (b) (4) is a Group 1 carcinogen as determined by IARC. Address why the increase in (b) (4) does not cause the new product to raise different questions of public health.

15. In SE0000282, SE0000283, SE0000284, SE0000285 and SE0000287, (b) (4) is used. Provide source and type of the (b) (4) (b) (4) used for the manufacturing of the new products. Address why the differences in (b) (4) do not cause the new products to raise different questions of public health.

At this time, the applicant has not responded to the scientific A/I letter or Preliminary Finding letter. Therefore, the applicant has not demonstrated that the new tobacco products do not raise different questions of public health from a toxicology perspective.

4.4. SOCIAL SCIENCE

A social science review was completed by Sarah Johnson on August 26, 2013.

The social science review concludes that all new products when compared to their predicate products have different characteristics, but the information submitted failed to demonstrate that the new products do not raise different questions of public health. Therefore, in the scientific A/I letter and Preliminary Finding letter, the following information was required:

16. In all of your SE Reports, the Health Information Summary contains statements that convey a modified exposure claim, referring to the new tobacco products, repeatedly, as (b) (4) (b) (4) Use of a claim such as this requires a market order based on a Modified Risk Tobacco Application under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used. Revise the Health Information Summary to remove references to the product as a (b) (4) product.

17. In all of your SE Reports, the (b) (4) of the new products differ from the corresponding predicate products, but no information was submitted to demonstrate that the new products do not raise different questions of public health (i.e., your new products do not have an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users). Submit information on the impact of these changes on initiation, cessation, and dependence. This information may include but is not limited to:

    - Consumer perception studies of the products, including its proposed marketing and labeling;
    - Taste panel results comparing the products with the predicate products;
    - Market analyses (e.g., sales and/or market segmentation analyses to identify likely consumers of the products); or
    - Other research and analyses conducted to prepare for the products' introduction into the marketplace.

At this time, the applicant has not responded to the scientific A/I letter or Preliminary Finding letter. Therefore, the applicant has not demonstrated that the new tobacco products do not raise different questions of public health from a social science perspective.

4.5. ADDICTION

An addiction review was completed by Kia Jackson on August 29, 2013.

The addiction review concludes that all new products when compared to their predicate products have different characteristics, but the information submitted failed to demonstrate that the new products do not raise different questions of public health. Therefore, in the scientific A/I letter and Preliminary Finding letter, the following information was required:

18. In SE0000286 and SE0000288, the (b) (4) is increased in the new products compared to the corresponding predicate products. Provide adequate scientific evidence, including use behaviors, demonstrating that the increased nicotine content does not cause the new products to raise different questions of public health relating to tobacco addiction.

19. In SE0000282, SE0000283 and SE0000287, the total (b) (4) (b) (4) is increased in the new products compared to the corresponding predicate products. In SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287, the HPHC (b) (4) (which has an addiction indication) has been added. Provide adequate scientific evidence, including use behaviors, demonstrating that the increased (b) (4) and addition of (b) (4) do not cause the new products to raise different questions of public health relating to tobacco addiction.

20. All of your SE Reports provide the pH values as "approximate" for both the new and predicate products. Provide more specific values and ranges instead of approximate values. Because pH alters nicotine absorption by altering free nicotine quantities, provide scientific evidence and rationale as to why differences in free nicotine, if they exist, do not cause the new products to raise different questions of public health.

21. In SE0000282, SE0000283, SE0000284, SE000285, SE0000287, the new products have differences in (b) (4) compared to the corresponding predicate products and the (b) (4) (b) (4) designed to make the new products less harsh and improve taste acceptability compared to the predicate products. Palatability influences initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. Provide adequate scientific evidence, clinical or nonclinical, demonstrating that these differences to the (b) (4) will not cause the new products to raise different questions of public health.

At this time, the applicant has not responded to the scientific A/I letter or Preliminary Finding letter. Therefore, the applicant has not demonstrated that the new tobacco products do not raise different questions of public health from an addiction perspective.

5. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by RADM David L. Ashley on November 19, 2013, based on a programmatic environmental assessment for agency determinations that products were not substantially equivalent. The programmatic environmental assessment was prepared by Hoshing Chang, Ph.D., dated November 14, 2013.

6. CONCLUSION AND RECOMMENDATION

The key differences between the new and corresponding predicate tobacco products are as follows:

- Change in the (all SE Reports)
- Changes in (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287 only)
- (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, and SE0000287 only)
- Increased level of tota (b) (4) (SE0000282, SE0000283, SE0000286, SE0000287, and SE0000288 only)
- Presence of (b) (4) (SE0000283, SE0000284, SE0000285, and SE0000287 only)
- Increased level of (b) (4) (SE0000286 only)
- (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, SE0000287, and SE0000288 only)
- Increased levels of (b) (4) (SE0000282, SE0000283, SE0000284, SE0000285, SE0000287, and SE0000288 only)

It is possible that there are other key differences between the new and predicate products that we were not able to identify because the applicant did not provide information outlined in the scientific A/I and Preliminary Finding letters.

The predicate tobacco products meet statutory requirements because the applicant has demonstrated them to be grandfathered products (i.e., they were shown to be commercially marketed in the United States as of February 15, 2007).

The new tobacco products do not meet the statutory requirements for a determination of substantial equivalence. All of the scientific reviews conclude the applicant has not demonstrated that the new tobacco products do not raise different questions of public health. Each review identified information omitted from the SE Reports that is required for determining whether the new and predicate tobacco products are substantially equivalent. In addition, all of the reviews captured concerns about the differences in characteristics between the new and predicate tobacco products and the information regarding those differences. A scientific A/I letter was issued and, because the applicant did not respond to the scientific A/I letter, a Preliminary Finding letter was issued. The applicant did not respond to

the Preliminary Finding letter. Therefore, given the outstanding deficiencies, the applicant has not adequately established that the new tobacco products do not raise different questions of public health. I recommend that NSE orders be issued.

The NSE order letters should be issued for the new tobacco products in SE0000282, SE0000283, SE0000284, SE0000285, SE0000286, SE0000287, and SE0000288, as identified on the cover pages of this review. It should be noted that the chemistry and addiction reviews both contained deficiencies regarding pH values and free nicotine levels. In the order letters, these two deficiencies are being combined into a single deficiency.

6.1. DEFICIENCIES FOR SE0000282

The NSE order letter for SE0000282 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report indicates that there are many changes in ingredients in terms of quantity or type or both. The new tobacco product includes (b) (4) (b) (4) and (b) (4) and (b) (4) than the predicate tobacco product. Additionally, the new tobacco product includes a (b) (4) (b) (4) These differences may affect the release rates and amounts of the tobacco constituents. However, evidence and scientific rationale is not provided to demonstrate that these differences do not cause the new tobacco product to raise different questions of public health.

4. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant

with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) would help in evaluating HPHC quantities in the new and predicate tobacco products.

5. Your SE Report provides two separate sets of nicotine data in (b) (4) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

6. Your SE Report provides TSNA quantities for the new tobacco product. (b) (4) and the TSNAs levels were reported as "NQ" for the predicate tobacco product. Several other HPHCs are presented as "NQ" and "BDL" (below the detection limit) as well. The data cannot be fully evaluated without complete information about the methodologies used to generate the HPHC data, including the limit of detection and limit of quantitation, accuracy and precision of the methods.

7. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

8. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

9. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including

the following information about the predicate and new tobacco products that is omitted in your SE Reports:

a. Target specification and upper and lower range limits for tobacco particle size (mm)
b. Target specification for portion weight (mg)
c. Upper and lower range limits for final tobacco moisture (%)
d. Upper and lower range limits for portion length (mm)
e. Upper and lower range limits for portion width (mm)
f. Upper and lower range limits for portion thickness (mm)

It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

10. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the test results is not provided for the following design parameters for the predicate tobacco product:

    a. Tobacco particle size (mm)
    b. Final tobacco moisture (%)
    c. Portion weight (mg)

    Certificates of analysis from the material supplier may provide such information.

11. Your SE Report indicates that there were substantial increases in several HPHCs, specifically (b) (4) . However, your SE Report did not include evidence and scientific rationale for why the increases in these HPHCs do not cause the new tobacco product to raise different questions of public health with regard to product toxicity.

12. Your SE Report indicates that the levels of carcinogenic compounds such as acetaldehyde, NNN, and NNK were reported for the new tobacco product but not for the predicate tobacco product. These chemicals are known to be carcinogenic. Without levels of these HPHCs in the predicate tobacco product, it cannot be determine whether or not the predicate and new tobacco products have different characteristics with regard to product toxicity.
13. Your SE Report indicates that (b) (4) is used in the new tobacco product but not the predicate tobacco product. However, your SE Report does not provide the source and type of the (b) (4) (b) (4) used for the manufacturing of the new tobacco product. Furthermore, your SE Report does not include evidence and scientific

rationale for why the presence of caramel coloring agent does not cause the new tobacco product to raise different questions of public health.

14. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as (b) (4) Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

15. Your SE Report indicates that the (b) (4) differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users).

16. Your SE Report indicates the (b) (4) is increased in the new tobacco product compared to the predicate tobacco product. (b) (4), which is an HPHC based, in part, on its potential to increase the addictiveness of nicotine, is increased in the new tobacco product. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences in HPHC levels do not cause the new tobacco product to raise different questions of public health with regard to consumer addiction.

17. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.

6.2. DEFICIENCIES FOR SE0000283

The NSE order letter for SE0000283 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and

supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report indicates that there are many changes in ingredients in terms of quantity or type or both. The new tobacco product includes (b) (4) Additionally, the new tobacco product includes a (b) (4) (b) (4) These differences may affect the release rates and amounts of the tobacco constituents. However, evidence and scientific rationale is not provided to demonstrate that these differences do not cause the new tobacco product to raise different questions of public health.

4. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) would help in evaluating HPHC quantities in the new and predicate tobacco products.

5. Your SE Report provides two separate sets of nicotine data in (b) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

6. Your SE Report provides TSNA quantities for the new tobacco product. However, the SE Report states (b) (4) and the TSNAs levels were reported as "NQ" for the predicate tobacco product. Several other HPHCs are presented as "NQ" and "BDL" (below the detection limit) as well. The data cannot be fully evaluated without complete information about the methodologies used to generate the HPHC data, including the limit of detection and limit of quantitation, accuracy and precision of the methods.

7. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

8. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

9. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including the following information about the predicate and new tobacco products that is omitted in your SE Reports:

    a. Target specification and upper and lower range limits for tobacco particle size (mm)
    b. Target specification for portion weight (mg)
    c. Upper and lower range limits for final tobacco moisture (%)
    d. Upper and lower range limits for portion length (mm)
    e. Upper and lower range limits for portion width (mm)
    f. Upper and lower range limits for portion thickness (mm)

    It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

10. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a

summary of the test results is not provided for the following design parameters for the predicate tobacco product:

a. Tobacco particle size (mm)
b. Final tobacco moisture (%)
c. Portion weight (mg)

Certificates of analysis from the material supplier may provide such information.

11. Your SE Report indicates that there were substantial increases in several HPHCs, specifically [redacted] However, your SE Report did not include evidence and scientific rationale for why the increases in these HPHCs do not cause the new tobacco product to raise different questions of public health with regard to product toxicity.

12. Your SE Report indicates that the levels of carcinogenic compounds such as acetaldehyde, NNN, and NNK were reported for the new tobacco product but not for the predicate tobacco product. These chemicals are known to be carcinogenic. Without levels of these HPHCs in the predicate tobacco product, it cannot be determine whether or not the predicate and new tobacco products have different characteristics with regard to product toxicity.

13. Your SE Report indicates that (b) (4) is used in the new tobacco product but not the predicate tobacco product. However, your SE Report does not provide the source and type of the (b) (4) (b) (4) used for the manufacturing of the new tobacco product. Furthermore, your SE Report does not include evidence and scientific rationale for why the presence of (b) (4) does not cause the new tobacco product to raise different questions of public health.

14. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as (b) (4) Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

15. Your SE Report indicates that the (b) (4) differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such

as initiation among non-users, or increased use or decreased cessation among users).

16. Your SE Report indicates the (b) (4) is increased in the new tobacco product compared to the predicate tobacco product. (b) (4), which is an HPHC based, in part, on its potential to increase the addictiveness of nicotine, is increased in the new tobacco product. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences in HPHC levels do not cause the new tobacco product to raise different questions of public health with regard to consumer addiction.

17. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.

6.3. DEFICIENCIES FOR SE0000284

The NSE order letter for SE0000284 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report indicates that there are many changes in ingredients in terms of quantity or type or both. The new tobacco product includes (b) (4) than the predicate

tobacco product. Additionally, the new tobacco product includes a (b) (4) (b) (4) These differences may affect the release rates and amounts of the tobacco constituents. However, evidence and scientific rationale is not provided to demonstrate that these differences do not cause the new tobacco product to raise different questions of public health.

4. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) would help in evaluating HPHC quantities in the new and predicate tobacco products.

5. Your SE Report provides two separate sets of nicotine data in (b) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

6. Your SE Report provides TSNA quantities for the new tobacco product. However, the SE Report states (b) (4) and the TSNAs levels were reported as "NQ" for the predicate tobacco product. Several other HPHCs are presented as "NQ" and "BDL" (below the detection limit) as well. The data cannot be fully evaluated without complete information about the methodologies used to generate the HPHC data, including the limit of detection and limit of quantitation, accuracy and precision of the methods.

7. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

8. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

9. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including the following information about the predicate and new tobacco products that is omitted in your SE Reports:

    a. Target specification and upper and lower range limits for tobacco particle size (mm)
    b. Target specification for portion weight (mg)
    c. Upper and lower range limits for final tobacco moisture (%)
    d. Upper and lower range limits for portion length (mm)
    e. Upper and lower range limits for portion width (mm)
    f. Upper and lower range limits for portion thickness (mm)

    It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

10. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the test results is not provided for the following design parameters for the predicate tobacco product:

    a. Tobacco particle size (mm)
    b. Final tobacco moisture (%)
    c. Portion weight (mg)

    Certificates of analysis from the material supplier may provide such information.

11. Your SE Report indicates that there were substantial increases in several HPHCs, specifically (b) (4) . However, your SE Report did not include evidence and scientific rationale for why the increases in these HPHCs do not cause the new tobacco product to raise different questions of public health with regard to product toxicity.

12. Your SE Report indicates that the levels of carcinogenic compounds such as acetaldehyde, NNN, and NNK were reported for the new tobacco product but not for the predicate tobacco product. These chemicals are known to be carcinogenic. Without levels of these HPHCs in the predicate tobacco product, it cannot be determine whether or not the predicate and new tobacco products have different characteristics with regard to product toxicity.

13. Your SE Report indicates that (b) (4) is used in the new tobacco product but not the predicate tobacco product. However, your SE Report does not provide the source and type of the (b) (4) (b) (4) used for the manufacturing of the new tobacco product. Furthermore, your SE Report does not include evidence and scientific rationale for why the presence of (b) (4) does not cause the new tobacco product to raise different questions of public health.

14. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as (b) (4) Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

15. Your SE Report indicates that the(of the new tobacco product differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users).

16. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.

6.4. DEFICIENCIES FOR SE0000285

The NSE order letter for SE0000285 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report indicates that there are many changes in ingredients in terms of quantity or type or both. The new tobacco product includes (b) (4) Additionally, the new tobacco product includes a (b) (4) These differences may affect the release rates and amounts of the tobacco constituents. However, evidence and scientific rationale is not provided to demonstrate that these differences do not cause the new tobacco product to raise different questions of public health.

4. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) would help in evaluating HPHC quantities in the new and predicate tobacco products.

5. Your SE Report provides two separate sets of nicotine data in (b) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data.

Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

6. Your SE Report provides TSNA quantities for the new tobacco product. However, the SE Report states (b) (4) and the TSNAs levels were reported as "NQ" for the predicate tobacco product. Several other HPHCs are presented as "NQ" and "BDL" (below the detection limit) as well. The data cannot be fully evaluated without complete information about the methodologies used to generate the HPHC data, including the limit of detection and limit of quantitation, accuracy and precision of the methods.

7. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

8. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

9. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including the following information about the predicate and new tobacco products that is omitted in your SE Reports:

    a. Target specification and upper and lower range limits for tobacco particle size (mm)
    b. Target specification for portion weight (mg)
    c. Upper and lower range limits for final tobacco moisture (%)
    d. Upper and lower range limits for portion length (mm)
    e. Upper and lower range limits for portion width (mm)
    f. Upper and lower range limits for portion thickness (mm)

    It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

10. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the test results is not provided for the following design parameters for the predicate tobacco product:

    a. Tobacco particle size (mm)
    b. Final tobacco moisture (%)
    c. Portion weight (mg)

    Certificates of analysis from the material supplier may provide such information.

11. Your SE Report indicates that there were substantial increases in several HPHCs, specifically (b) (4) . However, your SE Report did not include evidence and scientific rationale for why the increases in these HPHCs do not cause the new tobacco product to raise different questions of public health with regard to product toxicity.

12. Your SE Report indicates that the levels of carcinogenic compounds such as acetaldehyde, NNN, and NNK were reported for the new tobacco product but not for the predicate tobacco product. These chemicals are known to be carcinogenic. Without levels of these HPHCs in the predicate tobacco product, it cannot be determine whether or not the predicate and new tobacco products have different characteristics with regard to product toxicity.

13. Your SE Report indicates that (b) (4) is used in the new tobacco product but not the predicate tobacco product. However, your SE Report does not provide the source and type of the (b) (4) (b) (4) used for the manufacturing of the new tobacco product. Furthermore, your SE Report does not include evidence and scientific rationale for why the presence of (b) (4) does not cause the new tobacco product to raise different questions of public health.

14. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as (b) (4) Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

15. Your SE Report indicates that the (b) (4) of the new tobacco product differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users).

16. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.

6.5. DEFICIENCIES FOR SE0000286

The NSE order letter for SE0000286 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) would

help in evaluating HPHC quantities in the new and predicate tobacco products.

4. Your SE Report provides two separate sets of nicotine data in (b) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

5. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

6. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

7. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including the following information about the predicate and new tobacco products that is omitted in your SE Reports:

    a. Target specification and upper and lower range limits for tobacco particle size (mm)
    b. Target specification for portion weight (mg)
    c. Upper and lower range limits for final tobacco moisture (%)
    d. Upper and lower range limits for portion length (mm)
    e. Upper and lower range limits for portion width (mm)
    f. Upper and lower range limits for portion thickness (mm)

    It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

8. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the test results is not provided for the following design parameters for the predicate tobacco product:

    a. Tobacco particle size (mm)
    b. Final tobacco moisture (%)
    c. Portion weight (mg)

    Certificates of analysis from the material supplier may provide such information.

9. Your SE Report indicates that there were substantial increases in (b) (4), which is an HPHC. However, your SE Report does not include evidence and scientific rationale for why the increase in this HPHC does not cause the new tobacco product to raise different questions of public health.

10. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as (b) (4) Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

11. Your SE Report indicates that the (b) (4) of the new tobacco product differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users).

12. Your SE Report indicates that the (b) (4) is increased in the new tobacco product compared to the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale demonstrating that this difference does not cause the new tobacco product to raise different questions of public health.

13. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability

compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.

6.6. DEFICIENCIES FOR SE0000287

The NSE order letter for SE0000287 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report indicates that there are many changes in ingredients in terms of quantity or type or both. The new tobacco product includes (b) (4) Additionally, the new tobacco product includes a (b) (4) (b) (4) (b) (4) These differences may affect the release rates and amounts of the tobacco constituents. However, evidence and scientific rationale is not provided to demonstrate that these differences do not cause the new tobacco product to raise different questions of public health.

4. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a

summary of the results, standard deviations or confidence limits) would help in evaluating HPHC quantities in the new and predicate tobacco products.

5. Your SE Report provides two separate sets of nicotine data in (b) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

6. Your SE Report provides TSNA quantities for the new tobacco product. However, the SE Report states (b) (4) and the TSNAs levels were reported as "NQ" for the predicate tobacco product. Several other HPHCs are presented as "NQ" and "BDL" (below the detection limit) as well. The data cannot be fully evaluated without complete information about the methodologies used to generate the HPHC data, including the limit of detection and limit of quantitation, accuracy and precision of the methods.

7. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

8. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

9. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including the following information about the predicate and new tobacco products that is omitted in your SE Reports:

a. Target specification and upper and lower range limits for tobacco particle size (mm)
b. Target specification for portion weight (mg)
c. Upper and lower range limits for final tobacco moisture (%)
d. Upper and lower range limits for portion length (mm)
e. Upper and lower range limits for portion width (mm)
f. Upper and lower range limits for portion thickness (mm)

It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

10. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the test results is not provided for the following design parameters for the predicate tobacco product:

    a. Tobacco particle size (mm)
    b. Final tobacco moisture (%)
    c. Portion weight (mg)

    Certificates of analysis from the material supplier may provide such information.

11. Your SE Report indicates that there were substantial increases in several HPHCs, specifically (b) (4) . However, your SE Report did not include evidence and scientific rationale for why the increases in these HPHCs do not cause the new tobacco product to raise different questions of public health with regard to product toxicity.

12. Your SE Report indicates that the levels of carcinogenic compounds such as acetaldehyde, NNN, and NNK were reported for the new tobacco product but not for the predicate tobacco product. These chemicals are known to be carcinogenic. Without levels of these HPHCs in the predicate tobacco product, it cannot be determine whether or not the predicate and new tobacco products have different characteristics with regard to product toxicity.

13. Your SE Report indicates that (b) (4) is used in the new tobacco product but not the predicate tobacco product. However, your SE Report does not provide the source and type of the (b) (4) (b) (4) used for the manufacturing of the new tobacco product. Furthermore, your SE Report does not include evidence and scientific rationale for why the presence of (b) (4) does not cause the new tobacco product to raise different questions of public health.

14. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as (b) (4) Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

15. Your SE Report indicates that the (b) (4) of the new tobacco product differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users).

16. Your SE Report indicates the (b) (4) is increased in the new tobacco product compared to the predicate tobacco product. (b) (4), which is an HPHC based, in part, on its potential to increase the addictiveness of nicotine, is increased in the new tobacco product. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences in HPHC levels do not cause the new tobacco product to raise different questions of public health with regard to consumer addiction.

17. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.

6.7. DEFICIENCIES FOR SE0000288

The NSE order letter for SE0000288 should cite the following deficiencies:

1. Your SE Report lacks full characterization of all ingredients in all components and subcomponents. For example, the grade/purity and supplier of each ingredient would help fully characterize the new and predicate tobacco products.

2. Your SE Report provides the measured pH values for the new tobacco product but not for the predicate tobacco product. The percentage of free nicotine depends on the product pH, especially between pH 7 and 9. The measured pH values or the free nicotine levels based on measured pH values for the predicate tobacco product would help to demonstrate whether the new and predicate tobacco products are substantially equivalent.

3. Your SE Report provides average HPHC quantities, standard deviations, and 95% confidence limits for the new tobacco product. However, your SE Report only provides average HPHC quantities for the predicate tobacco product. We cannot determine whether the differences in HPHC quantities between the new and predicate tobacco products are significant with only the average values. Full test data (including test protocols, quantitative acceptance (pass/fail) criteria, national/international standards used and any deviation(s) from those standards, data sets, and a summary of the results, standard deviations or confidence limits) would help in evaluating HPHC quantities in the new and predicate tobacco products.

4. Your SE Report provides two separate sets of nicotine data in (b) (4) and (b) (4) reports. (b) (4) However, your SE Report did not provide an explanation for the discrepancies between the two sets of data. Additionally, the values reported in (b) (4) are reported in mg per gram unit with no indication of whether the values are as received or dry weight adjusted. It is not clear which nicotine data set to use for the determination of substantial equivalence.

5. Your SE Report lacks information about stability for the predicate and new tobacco products. Additional information about stability testing is needed to fully characterize the predicate and new tobacco products. Such information would include detailed stability testing, including test protocols, quantitative acceptance criteria, data sets and a summary of the results for all stability testing performed.

6. Your SE Report lists complex ingredients but does not distinguish between complex ingredients made to your specifications and those that are not. Furthermore, your SE Report lacks the information about complex ingredients made to your specifications as explained in FDA's *Guidance for Industry Listing of Ingredients in Tobacco Products*.

7. Your SE Report provides some information on the design parameters for the predicate and new tobacco products. However, your SE Report does not include all of the design parameters required to fully characterize the

predicate and new tobacco products. In order to adequately characterize the products, it is necessary to compare key design parameters, including the following information about the predicate and new tobacco products that is omitted in your SE Reports:

a. Target specification and upper and lower range limits for tobacco particle size (mm)
b. Target specification for portion weight (mg)
c. Upper and lower range limits for final tobacco moisture (%)
d. Upper and lower range limits for portion length (mm)
e. Upper and lower range limits for portion width (mm)
f. Upper and lower range limits for portion thickness (mm)

It is not clear if there are differences in these design parameters for the predicate and new tobacco product.

8. Your SE Report includes design parameter specifications but do not include raw data confirming that specifications are met. More specifically, the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria (pass/fail), data sets, and a summary of the test results is not provided for the following design parameters for the predicate tobacco product:

   a. Tobacco particle size (mm)
   b. Final tobacco moisture (%)
   c. Portion weight (mg)

   Certificates of analysis from the material supplier may provide such information.

9. Your SE Report indicates that there were substantial increases in several HPHCs, specificall (b) (4) . However, your SE Report does not include evidence and scientific rationale for why the increases in these HPHCs do not cause the new tobacco product to raise different questions of public health with regard to product toxicity.

10. Your SE Report includes a health information summary that contains statements which convey a modified exposure claim, referring to the new tobacco product repeatedly as "(b) (4) ." Use of a claim such as this requires a marketing order based on a Modified Risk Tobacco Product Application (MRTPA) under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act. Without such an order, this language cannot be used.

11. Your SE Report indicates that the (b) (4) of the new tobacco product differ from those of the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale for why the differences in (b) (4) do not cause the new tobacco product to raise different questions of public health (e.g., an impact on tobacco use behavior, such as initiation among non-users, or increased use or decreased cessation among users).

12. Your SE Report indicates that the (b) (4) is increased in the new tobacco product compared to the predicate tobacco product. However, your SE Report does not include evidence and scientific rationale demonstrating that this difference does not cause the new tobacco product to raise different questions of public health.

13. Your SE Report indicates that the new tobacco product has differences in (b) (4) compared to the predicate tobacco product. Also, the new tobacco product includes a (b) (4) designed to make the new tobacco product less harsh and improve taste acceptability compared to the predicate tobacco product. Palatability can influence initiation behaviors and abuse liability. In addition, these changes may alter release rate of tobacco constituents with addiction indications, thereby impacting product addictiveness. However, your SE Report does not include evidence and scientific rationale demonstrating that these differences do not cause the new tobacco product to raise different questions of public health.