FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0004825 - SE0004829 and SE0004875 - SE0004880

SE0004825: Red Seal Fine Cut Wintergreen	
Package Type	Plastic Can with Metal Lid
Package Quantity	42.53 grams
Tobacco Cut Size[1]	(b) and (b) Cuts Per Inch (CPI)
Characterizing Flavor	Wintergreen
SE0004826: Red Seal Long Cut Mint	
Package Type	Plastic Can with Metal Lid
Package Quantity	42.53 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	Mint
SE0004827: Red Seal Long Cut Natural	
Package Type	Plastic Can with Metal Lid
Package Quantity	42.53 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	None
SE0004828: Red Seal Long Cut Straight	
Package Type	Plastic Can with Metal Lid
Package Quantity	42.53 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	None
SE0004829: Red Seal Long Cut Wintergreen	
Package Type	Plastic Can with Metal Lid
Package Quantity	42.53 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	Wintergreen
SE0004875: Husky Fine Cut Natural	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size[1]	(b) and (b) CPI
Characterizing Flavor	None

[1] Applicant claimsthat the new product and predicate product have identical tobacco base comprised of 67.2% tobacco cut at (b) CPI and 32.8% tobacco cut at (b) CPI.

SE0004876: Husky Fine Cut Wintergreen	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size[1]	(b) and (b) CPI
Characterizing Flavor	Wintergreen
SE0004877: Husky Long Cut Mint	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	Mint
SE0004878: Husky Long Cut Natural	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	None
SE0004879: Husky Long Cut Straight	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	None
SE0004880: Husky Long Cut Wintergreen	
Package Type	Plastic Can with Metal Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	Wintergreen
Common Attributes of SE Reports	
Applicant	U.S. Smokeless Tobacco Company LLC
Report Type	Regular
Product Category	Smokeless Tobacco Products
Product Sub-Category	Loose Moist Snuff
Recommendation	
Issue Substantially Equivalent (SE) orders.	

Technical Project Lead (TPL):

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Date: 2019.06.27 14:12:38 -04'00'

Matthew J. Walters, Ph.D., MPH
CDR, U.S. Public Health Service
Deputy Director
Division of Product Science

Signatory Decision:

☒ Concur with TPL recommendation and basis of recommendation

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

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

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Date: 2019.06.28 08:15:28 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

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1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted the following predicate tobacco products:

SE0004825: Red Seal Fine Cut Wintergreen	
Product Name	Red Seal Fine Cut Wintergreen
Package Type	Plastic Can and Plastic Lid
Package Quantity	42.53 grams
Tobacco Cut Size[1]	(b) and (b) CPI
Characterizing Flavor	Wintergreen
SE0004826: Red Seal Long Cut Mint	
Product Name	Red Seal Long Cut Mint
Package Type	Plastic Can and Plastic Lid
Package Quantity	42.53 grams
Tobacco Cut Size[2]	(b) and (b) CPI
Characterizing Flavor	Mint
SE0004827: Red Seal Long Cut Natural	
Product Name	Red Seal Long Cut Natural
Package Type	Plastic Can and Plastic Lid
Package Quantity	42.53 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	None
SE0004828: Red Seal Long Cut Straight	
Product Name	Red Seal Long Cut Straight
Package Type	Plastic Can and Plastic Lid
Package Quantity	42.53 grams
Tobacco Cut Size[2]	(b) and (b) CPI
Characterizing Flavor	None
SE0004829: Red Seal Long Cut Wintergreen	
Product Name	Red Seal Long Cut Wintergreen
Package Type	Plastic Can and Plastic Lid
Package Quantity	42.53 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	Wintergreen

[2] Applicant claims that the predicate product has a tobacco base comprised of 70.1% tobacco cut at (b) CPI and 29.9% tobacco cut at (b) CPI.

SE0004875: Husky Fine Cut Natural	
Product Name	Husky Fine Cut Natural
Package Type	Plastic Can and Plastic Lid
Package Quantity	34.02 grams
Tobacco Cut Size[1]	(b) and (b) CPI
Characterizing Flavor	None
SE0004876: Husky Fine Cut Wintergreen	
Product Name	Husky Fine Cut Wintergreen
Package Type	Plastic Can and Plastic Lid
Package Quantity	34.02 grams
Tobacco Cut Size[1]	Not Provided
Characterizing Flavor	Wintergreen
SE0004877: Husky Long Cut Mint	
Product Name	Husky Long Cut Mint
Package Type	Plastic Can and Plastic Lid
Package Quantity	34.02 grams
Tobacco Cut Size[2]	(b) and (b) CPI
Characterizing Flavor	Mint
SE0004878: Husky Long Cut Natural	
Product Name	Husky Long Cut Natural
Package Type	Plastic Can and Plastic Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	None
SE0004879: Husky Long Cut Straight	
Product Name	Husky Long Cut Straight
Package Type	Plastic Can and Plastic Lid
Package Quantity	34.02 grams
Tobacco Cut Size[2]	(b) and (b) CPI
Characterizing Flavor	None
SE0004880: Husky Long Cut Wintergreen	
Product Name	Husky Long Cut Wintergreen
Package Type	Plastic Can and Plastic Lid
Package Quantity	34.02 grams
Tobacco Cut Size	(b) CPI
Characterizing Flavor	Wintergreen

The predicate tobacco products are loose moist snuff smokeless tobacco products manufactured by U.S. Smokeless Tobacco Company LLC.

1.2. REGULATORY ACTIVITY

FDA received 11 SE Reports on August 8, 2012, and August 30, 2012, from Altria Client Services Inc. (ALCS) on behalf of U.S. Smokeless Tobacco Company LLC (USSTC). On August 30, 2012, FDA received amendments (SE0004870 – SE0004874) for SE0004825 – SE0004829 which contained additional information inadvertently omitted from the original SE Reports. FDA issued Acknowledgement letters on September 7, 2012, and October 2, 2012. On December 28, 2012, FDA issued an Advice/Information Request (A/I) letter requesting additional product information for all of the new and predicate tobacco products, a statement of compliance with Section 907, and an environmental assessment. On January 24, 2013, FDA received amendments (SE0006669, SE0006696 – SE0006701, SE0007943, SE0007944, and SE0007947, and SE0007948) for all SE Reports, which contained responses to the December 28, 2012, A/I letter. On April 3, 2013, FDA called the applicant (April 3, 2013, and April 5, 2013) for clarification of package type and size/weight of the new and predicate tobacco products. On April 5, 2013, FDA received amendments (SE0008165, SE0008173, SE0008175, and SE0008177 – SE0008184) for all SE Reports, which contained requested information on package type and size/weight of products. FDA issued a Notification letter on April 30, 2013, to inform the applicant that substantive scientific review was to begin 45 days from the date of the letter on June 14, 2013. On May 14, 2013, FDA received amendments (SE0008541 – SE0008546) for SE0004875 – SE0004880 to replace the information received on April 5, 2013. On May 29, 2013, FDA received amendments (SE0008686 – SE0008688, SE0008690, SE0008692, SE0008694, SE0008714, SE0008715, SE0008717, SE0008718, and SE0008724) for all SE Reports, which contained an environmental assessment. On June 13, 2013, FDA received amendments (SE0008995, SE0008996, and SE0008998 – SE0009001) for SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878, which contained a correction to the Ingredients Comparison section of the original submission.

FDA issued an A/I letter to the applicant on December 30, 2013. On January 27, 2014, FDA received an amendment (SE0010130) for all SE Reports, which contained a request for an extension to provide a response to the December 30, 2013 A/I letter. On February 4, 2014, FDA issued an Extension Response letter requesting additional information in order to adequately assess and respond to the extension request. FDA received amendments (SE0010158 – SE0010162 and SE00010164) for SE0004875 – SE0004880 on February 4, 2014, which contained a correction to product weight provided in the April 5, 2013, amendments. On February 7, 2014, FDA received an amendment (SE0010172) for all STNs, which contained a response to the Extension Response letter dated February 4, 2014, and subsequently, FDA issued an Extension Granted letter on February 14, 2014, with an extended response date of April 14, 2014, to respond to the December 30, 2013, A/I letter. On April 11, 2014, FDA received amendments (SE0010385 – SE0010396) for all SE Reports, which contained responses to the A/I letter dated December 30, 2013. On August 22, 2014, FDA received amendments (SE0010649 – SE0010651) for SE0004877, SE0004879, and SE0004880, which contained updates to the responses received on April 11, 2014. On February 10, 2015, FDA received amendments (SE0010903, SE0010904, SE0010906 – SE0010909) for SE0004825, SE0004827 – SE0004829, SE0004875, and SE0004878, which contained a correction to the Ingredient Table provided in the original submission. On September 6, 2016, FDA issued a Preliminary Finding letter to the applicant. On September 13, 2016, FDA received a call from the applicant requesting clarification on an item listed in the Preliminary Finding letter which was responded to by FDA via email. On October 5, 2016, FDA received an amendment (SE0013719) for all SE Reports, which contained a response to the Preliminary Finding letter dated September 6, 2016. On October 20, 2016, FDA received an amendment (SE0013731) for all SE

Reports, which contained analysis of tobacco specific nitrosamines and nicotine. On August 25, 2017, after all scientific reviews were completed (except Behavioral and Clinical Pharmacology review), FDA received unsolicited amendments (SE0014263 – SE0014269, SE0014271 and SE0014276 – SE0014277) for SE0004825 – SE0004829 and SE0004875 – SE0004879, which contained corrected ingredient table values for the predicate tobacco products. Although FDA received this amendment after the response due date, the technical project lead (TPL) conducted a review of the amendments (SE0014263 – SE0014269, SE0014271 and SE0014276 – SE0014277) in conjunction with the TPL's review of all information submitted by the applicant as review of this amendment (received in August 2017) does not further delay FDA's continued review of these SE Report. The TPL determined that the August 25, 2017, amendment does not alter the conclusions of the final scientific reviews or this TPL review because the amendment corrected an insignificant amount of (b) (4), an ingredient, in the predicate tobacco products. The information previously reported that this ingredient was present in the predicate tobacco products at (b) (4) , and the corrected information indicated that this ingredient is in the predicate tobacco products in amounts of (b) (4) . This difference does not alter the conclusions of the finalized scientific reviews. On March 6, 2018, a telecon was held requesting the applicant to submit the characterizing flavors for the new and predicate tobacco products. Subsequently, on March 6, 2018, FDA received an amendment (SE0014567) stating the following: both the new and predicate tobacco products for SE0004825, SE0004829, SE0004876, and SE0004880 are wintergreen; both the new and predicate tobacco products for SE0004826 and SE0004877 are mint; and both the new and predicate tobacco products for SE0004827, SE0004828, SE0004875, SE0004878, and SE0004879 are none. The TPL determined that the March 6, 2018, amendment does not alter the conclusions of the final scientific reviews as the applicant was only clarifying which tobacco products contained a characterizing flavor and which tobacco products did not which was previously captured in the scientific reviews.

Product Name	SE Report	Amendments
Red Seal Fine Cut Wintergreen	SE0004825	SE0004870 SE0007947 SE0008173 SE0008714 SE0008998 SE0010130 SE0010172 SE0010386 SE0010396 SE0010903 SE0013719 SE0013731 SE0014269 SE0014567
Red Seal Long Cut Mint	SE0004826	SE0004871 SE0007943 SE0008177 SE0008715 SE0010130 SE0010172 SE0010385 SE0010396 SE0013719 SE0013731 SE0014271 SE0014567
Red Seal Long Cut Natural	SE0004827	SE0004872 SE0007944 SE0008178 SE0008717 SE0008999 SE0010130 SE0010172 SE0010387 SE0010396 SE0010904 SE0013719 SE0013731 SE0014265 SE0014567

Red Seal Long Cut Straight	SE0004828	SE0004873 SE0007948 SE0008179 SE0008718 SE0010130 SE0010172 SE0010391 SE0010396 SE0010908 SE0013719 SE0013731 SE0014268 SE0014567
Red Seal Long Cut Wintergreen	SE0004829	SE0004874 SE0006696 SE0008180 SE0008724 SE0008995 SE0010130 SE0010172 SE0010389 SE0010396 SE0010906 SE0013719 SE0013731 SE0014266 SE0014567
Husky Fine Cut Natural	SE0004875	SE0006697 SE0008165 SE0008541 SE0008686 SE0008996 SE0010130 SE0010159 SE0010172 SE0010390 SE0010396 SE0010909 SE0013719 SE0013731 SE0014267 SE0014567

Husky Fine Cut Wintergreen	SE0004876	SE0006698 SE0008175 SE0008542 SE0008687 SE0009000 SE0010130 SE0010158 SE0010172 SE0010388 SE0010396 SE0013719 SE0013731 SE0014264 SE0014567
Husky Long Cut Mint	SE0004877	SE0006699 SE0008181 SE0008543 SE0008688 SE0010130 SE0010160 SE0010172 SE0010394 SE0010396 SE0010650 SE0013719 SE0013731 SE0014263 SE0014567
Husky Long Cut Natural	SE0004878	SE0006701 SE0008182 SE0008544 SE0008694 SE0009001 SE0010130 SE0010161 SE0010172 SE0010393 SE0010396 SE0010907 SE0013719 SE0013731 SE0014276 SE0014567

Husky Long Cut Straight	SE0004879	SE0006700 SE0008183 SE0008545 SE0008690 SE0010130 SE0010162 SE0010172 SE0010392 SE0010396 SE0010651 SE0013719 SE0013731 SE0014277 SE0014567
Husky Long Cut Wintergreen	SE0004880	SE0006669 SE0008184 SE0008546 SE0008692 SE0010130 SE0010164 SE0010172 SE0010395 SE0010396 SE0010649 SE0013719 SE0013731 SE0014567

1.3. SCOPE OF REVIEW

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

2. REGULATORY REVIEW

Regulatory reviews were completed by Atasi Poddar on December 28, 2012, April 4, 2013 for SE0004825 – SE0004828, October 2, 2012 for SE0004875 – SE0004880 and February 27, 2013 for SE0004829, and SE0004875 – SE0004880.

The final reviews note that environmental assessments were not included in the original submissions. On May 29, 2013, the applicant submitted environmental assessments for all SE Reports.

The regulatory review completed by Sarah Hernandez on August 22, 2017 concludes that the SE Reports are administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews to determine whether the applicant established that the predicate tobacco products are grandfathered products (i.e., were commercially marketed in the United States other than exclusively in test markets as of February 15, 2007). The OCE reviews[3,4] dated May 22, 2013, for SE0004875, SE0004876, and SE0004880; May 31, 2013, for SE0004825 – SE0004829 and SE0004877 – SE0004879; March 10, 2014 for SE0004877 – SE0004880; and March 12, 2014 for SE0004875 – SE0004876, conclude that the evidence submitted by the applicant is adequate to demonstrate that the predicate tobacco products are grandfathered and, therefore, are eligible predicate tobacco products.

OCE also completed a review to determine whether the new tobacco products are in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act) (see section 910(a)(2)(A)(i)(II) of the FD&C Act). The OCE review dated June 17, 2019, concludes that the new tobacco products are in compliance with the FD&C Act.

4. SCIENTIFIC REVIEW

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

4.1. CHEMISTRY[5]

Chemistry reviews were completed by Katherine Lovejoy on October 3, 2013, and June 26, 2014, and Robert Gahl on November 21, 2016.[6]

The final chemistry review concludes that the new tobacco products have different characteristics related to product chemistry compared to the corresponding predicate tobacco products and that the SE Reports lack adequate evidence to demonstrate that the differences do not cause the new tobacco products to raise different questions of public health. The review identifies the following deficiencies[7] that have *not* been adequately resolved:

1. SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878 provide some information about tobacco and ingredients added to the surrogate tobacco products. However, your SE Reports do not include all ingredients in all components of the surrogate

[3] An addendum review was completed on April 6, 2018, to clarify the characterizing flavor of the predicate tobacco product. The addendum review does not change the conclusion of the initial grandfather determinations dated May 22, 2013, and May 31, 2013.
[4] An addendum review was completed on March 10, 2014, and on March 12, 2014, to clarify weight information of the predicate tobacco product. The addendum review does not change the conclusion of the initial grandfather determinations dated May 22, 2013, and May 31, 2013.
[5] The applicant provided surrogate tobacco products for the predicate products for SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878; as TPL, however, the applicant provided adequate information to allow extrapolation of information for the surrogate predicate tobacco products to that of the predicate tobacco products. The applicant provided surrogate tobacco products for the new tobacco products in all SE Reports subject of this TPL review. The chemistry information for the surrogate new tobacco products was sufficient to allow extrapolation to that of the new tobacco products. The key difference between the new and surrogate new tobacco products was a difference in the container closure system.
[6] An addendum dated September 21, 2017, updated and corrected the finalized chemistry review dated November 21, 2016.
[7] The addition of menthol was reviewed by chemistry, but deferred to toxicology, which at the time of the review was OS' policy. The chemistry discipline noted the increase in menthol and the potential impact that this increase may have on toxicology, and toxicology evaluated this increase in the toxicology review.

predicate products. Without this information, we cannot determine whether the predicate and new products are substantially equivalent. Additionally, the information provided for tobacco and ingredients does not include sufficient detail to fully identify the composition of the predicate and new products. We need any other information you may have that uniquely identifies the tobacco used in the surrogate predicate products. This is the information that you rely on to ensure that the tobacco used in the predicate and new products is equivalent for both products. For example, if you use a tobacco grading system, it would be helpful to know the tobacco grade (along with an explanation of the grading system) for each type of tobacco used in the predicate and new products. Similarly, for other ingredients, it would be helpful to know the grade of each ingredient. Provide a detailed list including:

a. Ingredients for all components
b. Uniquely identifying information for all tobacco (e.g., tobacco grading system)
c. Uniquely identifying information for all ingredients (e.g., CAS #, grade/purity, function)

In addition to the ingredient information, HPHC (i.e., NNN, NNK, and nicotine) information and pH values comparing the surrogate tobacco products to the new and predicate products needs to also be submitted.

If a difference exists between the surrogate for the new and corresponding surrogate predicate products, provide a rationale for each difference with evidence and a scientific discussion for why the difference does not cause the new product to raise different questions of public health.

2. SE0004825 – SE0004829, SE0004875 – SE0004880 show discrepancies between the total HPHC amount from the dissolution study and measured amounts in the new and predicate products. For example, SE0004825 and SE0004877 show an increased dissolution of NNN and NNK in the new products compared to the corresponding predicate or surrogate products; however, the NNN and NNK levels in these new products (dry weight) showed decreases compared to the corresponding predicate products. Furthermore, the total measured NNN and NNK levels in all the dissolution runs only account for 30 – 41% of the total NNN or NNK in the new and predicate tobacco products. The total nicotine measured in the dissolution study for some SE Reports were greater than 100% of the amount in the new and predicate products. Explain these discrepancies.

3. SE0004825 – SE0004829, SE0004875 – SE0004880 state that the final pH values of the predicate products range from 7.41 to 7.64, while the final pH values of the new products range from 7.56 to 7.87. This range is within the most sensitive part of the protonated/unprotonated nicotine ratio curve. Therefore, the new products have free nicotine concentrations ranging from 3.19 – 4.86 mg/product, which is an 18 – 88% increase from the free nicotine concentrations in the predicate product (2.48 – 3.63 mg/product). Provide scientific evidence and rationale as to why this increase of free nicotine in the new products does not cause the new products to raise different questions of public health.

Therefore, the review concludes that the applicant did not demonstrate that the differences in characteristics between the new and corresponding predicate tobacco products do not cause

the new tobacco products to raise different questions of public health from a chemistry perspective.

As TPL, I disagree with the assessment of the chemistry reviewer. The chemistry reviewer indicates that the applicant has not provided adequate information on the surrogate predicate tobacco products. However, the applicant indicates that the surrogate predicate tobacco products are identical to the predicate tobacco products with the exception of small ingredient differences attributable to the "small amount of (b) (4)." The applicant further explains that the "small (b) (4) amount of (b) (4)" is composed of (b) (4) which is not in the predicate tobacco product. In this case, given that these differences between the predicate and surrogate predicate tobacco products are small, these differences do not prevent extrapolation of information from the surrogate predicate tobacco products to that of the predicate tobacco products. As TPL, the statement provided within the submission is adequate indicating that the predicate and surrogate predicate tobacco products are identical with the exception, as noted above, related to (b) (4). Therefore, as TPL, deficiency 1 should not conveyed to the applicant as the applicant has provided information to satisfy this concern and the surrogate predicate tobacco products are acceptable.

Additionally, as TPL, I disagree with deficiency 2 and deficiency 3 as assessed by the chemistry reviewer. In this case, the higher amounts of pH modifiers (e.g., (b) (4)), the change in target pH, and the higher amount of calculated free nicotine in the new tobacco products are related.[8] The changes in pH between the new and corresponding predicate tobacco products are within the most sensitive part of the protonated and unprotonated (free-base) nicotine ratio curve in which nicotine would be susceptible to different protonation states. The chemistry reviewer, however, was unable to conclude in this case that the calculate increase in free nicotine does not raise different questions of public health from a chemistry perspective. However, I as TPL, disagree with this assessment. In this case, a finding that the free nicotine increase in the new tobacco products does not raise different questions of public health would also indicate that the changes in pH and changes in the pH modifiers in the new tobacco products similarly do not raise different questions of public health from a chemistry perspective. The chemist assessed these differences but deferred the decision of whether changes in pH in the new tobacco products, which led to a calculated increase of free nicotine and the measured increase in total nicotine in the dissolution studies, to Behavioral and Clinical Pharmacology (BCP) for further evaluation of the effects of these changes on the user. The chemistry reviewer also identified in deficiency 2 that there were concerns with the dissolution studies, specifically to the measurements of dissolved NNN and NNK. The chemistry review concluded the total measured NNN and NNK levels in all the dissolution runs only account for 30 – 41% of the total NNN or NNK in the new and predicate tobacco products. However, the dissolution studies are not appropriate to demonstrate that differences in NNN/NNK do not raise different questions of public health as the primary toxicological concern is with the total amounts of NNN/NNK and not the NNN/NNK release as

[8] In the simplest case, a change in the relative amounts of the acidic (b) (4)), basic (i.e., (b) (4)), and counter ion (b) (4) [Note that (b) (4) does not change the pH but serves to maintain the pH buffer created by the combination of the acidic and basic modifiers) pH modifiers in an ingredient mixture will lead to a change in the pH of the tobacco product. When exposed to moisture (like the inside of the mouth or in a dissolution vessel), the pH modifiers will change the pH of the immediate solution. An increase in pH will cause nicotine in solution to de-protonate to form "free" nicotine. At the target pH stated by the applicant, small changes in pH may lead to large changes in free nicotine.

determined by the dissolution studies. Furthermore, the total amounts of NNN/NNK in the new and corresponding predicate tobacco products are small, which can lead to the inconsistencies in measurements of dissolved NNN and NNK as described in deficiency 2. The chemistry reviewer should have been concerned with total TSNA amounts in the new tobacco products which should have been the appropriate analysis and in this case, toxicology found that the total TSNA amounts in the new tobacco products were decreased as compared to the corresponding predicate tobacco products. Therefore, deficiency 2 should not be conveyed to the applicant. As discussed in section 4.4, the toxicology evaluation found that the decreases in the NNN and NNK quantities between the new and predicate tobacco products do not cause the new tobacco products to raise different questions of public health.

The new and the corresponding predicate tobacco products are loose moist snuff smokeless tobacco products. To demonstrate that the differences between the new and corresponding predicate tobacco products do not affect the nicotine release characteristics, the applicant provided nicotine dissolution profiles of the new and corresponding predicate tobacco products, which indicate that the nicotine release rates are statistically equivalent. From the chemistry perspective, the focus of comparison of two nicotine dissolution profiles is on the initial 4-6 timepoints, which roughly equate to the time period encompassing the rate of the initial rise of nicotine absorption in Pharmacokinetic (PK) studies.[9] These timepoints are used to calculate the difference factor f_1 and similarity factor, f_2. These factors are used when comparing two dissolution data sets (one average dissolution curve for the new tobacco product and one average dissolution curve for the predicate tobacco product). When comparing two dissolution profiles, an f_1 value of 0-15 and f_2 value between 50 and 100 demonstrates that the two curves are similar. Accordingly, based on a f_1/f_2 analysis of the dissolution data set, I find that the nicotine release rates for the new and corresponding predicate tobacco products are considered equivalent. Therefore, as TPL, I find that as nicotine dissolution and the changes in pH and pH modifiers are related to each other as discussed above and the dissolution profiles are similar indicating that the release rates are similar, no further information from the applicant on these issues is needed. As such, deficiency 2 and deficiency 3 should not be conveyed to the applicant. Therefore, the different characteristics related to product chemistry between the new tobacco products and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health.

4.2. ENGINEERING

Engineering reviews were completed by Christian Coyle on September 30, 2013, Christopher Brown on June 26, 2014, and Julie Morabito on November 16, 2016.

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

[9] The f_1/f_2 analysis only takes into account data points encompassing up to 85% nicotine dissolution. In the case of the new and predicate tobacco products, this threshold encompasses approximately the first 15-30 minutes (i.e., the initial 4-6 timepoints). Accordingly, the f_1/f_2 analysis for the new and predicate tobacco products evaluated the initial timepoints that comprise the fastest changing portions of the products' respective nicotine dissolution curves.

1. All of your SE Reports provide some, but not all, of the information needed regarding the design parameter specifications for tobacco cut size and information confirming that tobacco cut size specifications have been met for the new and corresponding predicate products. Provide the cut size and information confirming that the tobacco cut size specifications have been met for the new and corresponding predicate products.

   SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878 provide manufacturing process information for the surrogate predicate products. However, due to differences in tobacco blend composition and/or processing steps compared to the predicate products, the surrogate predicate products are not appropriate surrogate products and cannot be used for comparison with the new products for SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878. You may submit design parameter data for products other than the predicate product (referred to as surrogate tobacco product) that can be extrapolated to the predicate product. In this case, data for the surrogate tobacco product could be submitted in place of data for the predicate product. However, information and data need to be provided to demonstrate that data for the surrogate tobacco product can be extrapolated to the predicate product. For example, the design parameters specifications for the predicate and surrogate product should be compared and an explanation provided for how each difference in specification would affect the extrapolation from the surrogate to predicate products.

   SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880 provide a detailed side-by-side comparison of the manufacturing process, which indicates that there are differences in the manufacturing process and tobacco blend composition between the new products and corresponding predicate products. The comparison includes information on the step-by-step cutting and sieving process, but does not include a justification for why the differences in processing do not cause any differences in the tobacco cut size. As such, the comparison is not sufficient to demonstrate that there is or is not a difference in tobacco cut size between the new and corresponding predicate products. Differences in tobacco cut size may influence constituent yields of the new products by altering constituent dissolution rates. Therefore, provide scientific rationale to demonstrate that any difference in tobacco cut size between the new and corresponding predicate products for all SE Reports do not cause the new products to raise different questions of public health.

   For SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880, show there are more than minor differences in manufacturing process (i.e. change in cutter size setting, sieving equipment used, or other relevant process parameter) between the new and corresponding predicate products, one way to satisfy this deficiency would be to manufacture the new product consistent with current product composition and design specifications and remanufacture the predicate product consistent with the product composition and design specifications in place at the time the grandfathered predicate product was originally manufactured. Then test the particle size of the new product and the remanufactured predicate product and submit the data for comparison of particle size. Another option would be to select a tobacco blend and subject it to the new product manufacturing process, then use the identical tobacco blend and subject it to the predicate product manufacturing process. After both batches have been through their respective process, test the products from both the new product manufacturing process and the predicate product

manufacturing process for tobacco cut size and submit the data for comparison of tobacco cut size. There may be other ways to address this deficiency. You are responsible for providing the evidence and scientific rationale to establish substantial equivalence.

Also, because particle size can affect constituent release, a scientific rationale is necessary to demonstrate why any differences in tobacco cut size between the new and corresponding predicate products do not cause the new products to raise different questions of public health.

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

As stated previously in Section 4.1, as TPL, I have concluded that the applicant provided sufficient information to demonstrate that data from the surrogate predicate tobacco products can be extrapolated to the predicate tobacco products in SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878. The applicant also provided sufficient information to demonstrate that data from the surrogate new tobacco products can be extrapolated to the new tobacco products in these SE Reports. The applicant did not provide a target value for the tobacco cut size for the new and corresponding predicate tobacco products; however, they stated that the following tobacco cutting parameters are identical between the new and corresponding predicate tobacco products: tobacco blend composition, machine cutter setting, the number of cuts, the sieve mesh, and the milling. In this case, FDA determined that no additional information regarding tobacco cut size was necessary as identical tobacco cutting parameters are used to manufacture the surrogate new and surrogate predicate tobacco products and are unlikely to result in differences in tobacco cut size between the surrogate new tobacco products and the corresponding surrogate predicate tobacco products; the applicant adequately demonstrated that it is unlikely that any difference would exist between the tobacco cut size of the new and corresponding predicate tobacco products in SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878. However, the tobacco cutting parameters provided by the applicant are not identical between the new and corresponding predicate tobacco products in SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880. Differences in tobacco cut size can affect constituent release. The applicant provided nicotine dissolution data and NNN and NNK quantities, which were deferred to chemistry for further evaluation. In this case, the applicant has demonstrated that nicotine release rates are analytically equivalent between the new and predicate tobacco products. Additionally, as discussed in Section 4.1, dissolution studies are not appropriate to demonstrate that differences in NNN/NNK do not raise different questions of public health as the primary toxicological concern is with the total amounts of NNN/NNK, not the NNN and NNK dissolution rates, and the toxicology evaluation found that there were decreases in the NNN and NNK quantities between the new and predicate tobacco products and concluded that these differences do not cause the new tobacco products to raise different questions of public health. Given the measured decreases in total NNN and NNK quantities in the new tobacco products, any changes in tobacco cut size in this case do not cause the new tobacco products in SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880 to raise different questions of public health.

Therefore, the differences in characteristics related to product engineering between the new tobacco products and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health.

4.3. MICROBIOLOGY

Microbiology reviews were completed by Norma Duran on November 12, 2013, Shanil Haugen on June 11, 2014, and Prashanthi Mulinti on November 16, 2016.

The final microbiology review concludes that the new tobacco products have different characteristics related to product microbiology compared to the corresponding predicate tobacco products but the differences do not cause the new tobacco products to raise different questions of public health. The review identified the following differences:

- Different container closure system: plastic can with a metal lid instead of a plastic can with a plastic lid
- Addition of the preservative (b) (4) [redacted]

Although differences in container closure system materials might result in different moisture levels (and thus different levels of bacterial growth), the applicant demonstrated that pH, water activity, and moisture content have limited variability over the storage time; thus, the change in container closure system materials does not cause the new tobacco product to raise different questions of public health. The applicant also demonstrated that the addition of the preservative resulted in stable levels of nitrate, NNN, NNK, and total TSNAs over time. Therefore, the review concludes that there was adequate information from a microbiology perspective to determine that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health.

4.4. TOXICOLOGY

Toxicology reviews were completed by Hans Rosenfeldt on December 24, 2013, Mary Kushman on July 28, 2016, and Wanyoike Kang'ethe on November 28, 2016.[10]

The final toxicology review concludes that the new tobacco products have different characteristics related to product toxicology compared to the corresponding predicate tobacco products but the differences do not cause the new tobacco products to raise different questions of public health. The review identified the following differences:

- Different container closure system: plastic can with a metal lid instead of a plastic can with a plastic lid

[10] An addendum dated June 5, 2019 updated the finalized toxicology review dated November 28, 2016 to clarify the discussion and evaluation regarding menthol as a permeation enhancer for SE0004877 and SE0004826.

- Addition of the preservative (b) (4)
- Addition of menthol in SE0004877 due to the addition of the (b) (4)
- 255% increase of menthol in SE0004826 due to the addition of the (b) (4) l
- Decrease in total TSNAs, NNN, and NNK ranging from 6% - 45%

All the new tobacco products use metal lids that are (b) (b) (4) whereas the corresponding predicate tobacco products use plastic lids. (b) (4) ingredients could transfer or undergo chemical or physical changes that impact the characteristics of the tobacco products. However, the coating extraction testing provided by the applicant demonstrated that the (b) (b) (4) did not become part of or impact the new tobacco products. As such, the use of (b) (4) metal lids in the container closure system for these new tobacco products does not cause the new tobacco products to raise new questions of public health. The new tobacco products contain an addition of (b) (4) at a concentration (b) (4) of smokeless tobacco. The (b) (4) levels added translate to daily intake levels of up to (b) (4) /day, factoring additional dietary exposure, which is only slightly higher when compared to the predicate tobacco products. Such levels of exposure are below WHO and EPA guidelines (0.03 mg/kg/day for both) that appear to be adequately protective for thyroidal effects, which are the most sensitive toxicological endpoint. Thus, the addition of (b) (4) to the new tobacco products at the indicated levels is not expected to result in additional toxicity that would cause the new tobacco products to raise different questions of public health as compared to the corresponding predicate tobacco products.

For SE0004877 and SE0004826, there was an addition of menthol in SE0004877 and a 255% increase in SE0004826 due to changes in the amounts of (b) (4) " used. The increase or addition of menthol could result in the permeation of HPHCs as menthol can act as a permeation enhancer. However, when comparing the tobacco-specific nitrosamines (TSNAs) levels between the surrogate new tobacco products and the predicate tobacco products, the NNN and NNK content decreased in the surrogate new tobacco products. In SE0004826, NNN and NNK content in the surrogate new tobacco product decreased by 40% and 15% respectively, relative to the predicate tobacco product. In SE0004877, the NNN and NNK content in the surrogate new tobacco product decreased by 42% and 24% respectively, relative to the predicate tobacco product. The surrogate new tobacco products are identical to the new tobacco products in every aspect except the container closure system; thus, data from the surrogate new tobacco products can be extrapolated to the new tobacco products. Considering that NNN and NNK are the main drivers of toxicity in smokeless tobacco products, and that no other HPHC increases were reported, the toxicological risk from increased toxicant exposure attributable to the higher menthol levels is likely offset by the lower TSNA content in the new tobacco products in SE0004877 and SE0004826. Therefore, the increase or addition of (b) (4) to the new tobacco products at the indicated levels for these SE Reports does not cause the new tobacco products to raise different questions of public health. Therefore, the differences in characteristics between the new and corresponding predicate

tobacco products do not cause the new tobacco products to raise different questions of public health from a toxicology perspective.

4.5. SOCIAL SCIENCE

Social science reviews were completed by Amber Koblitz on September 23, 2013[11] and June 30, 2014. An addendum to the September 23, 2013, review was completed on December 20, 2013 for SE0004875 – SE0004880.[12]

The final social science review concludes that the new tobacco products have different characteristics from a social science perspective compared to the corresponding predicate tobacco products but the differences do not cause the new tobacco products to raise different questions of public health. The review identified the following difference:

- Different flavoring ingredients in the new tobacco products for SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880

Although some of the new tobacco products contain different flavoring ingredients than the corresponding predicate tobacco products, the characterizing flavor of the new and predicate tobacco products is unchanged. For example, despite the different flavoring ingredients, the characterizing flavor of both the new and predicate tobacco products in SE0004826 is mint. Thus, from a social science perspective, the different flavoring ingredients in the new tobacco products do not raise different questions of public health. As TPL, I agree with the social science review. The social science review states there is insufficient evidence to conclude that these differences influence tobacco use behaviors such as dependence, initiation among non-users, or increased use or decreased cessation among users; thus, based on currently available evidence, changes in flavoring ingredients where the overall characterizing flavor of the new tobacco product as compared to the predicate tobacco product is unchanged, such as in this case, does not cause the new tobacco product to raise different questions of public health from a social science perspective. Therefore, I conclude that at this time, there is adequate information from a social science perspective to determine that the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health. Additionally, the final social science review states that there is no evidence to suggest that the addition of a similarly flavored product to other products in the applicant's portfolio, would impact tobacco use behavior. It is important to clarify that this comparison is not relevant to the review of SE Reports, as the basis for determination of substantial equivalence must be a one-to-one comparison of the new tobacco product to a predicate tobacco product, not to the marketplace. This was written in error.

[11] This review evaluated the name of the new tobacco product, which at the time of the review was OS' policy; however, this information was not considered in determining the substantial equivalence of these SE Reports.

[12] The December 20, 2013 addendum identified decreases in product quantity for SE0004875-SE0004880. The reviewer requested information from the applicant to demonstrate that a decrease in product quantity does not cause the new product to raise different questions of public health, which at the time of the addendum was OS' policy. The applicant responded with amendments SE0010158 – SE0010162 and SE00010164 which corrected the product weight. With this amendment, the product quantity of the new and predicate tobacco products is identical and no further information is needed to address this request.

The review also evaluated the health information summary for each SE Report. FDA has determined that the health information summaries provided for these SE Reports would not cause a violation of section 911 of the FD&C Act upon introduction or delivery for introduction of the new tobacco product into interstate commerce.

4.6. BEHAVORIAL AND CLINCIAL PHARMACOLOGY

A Behavioral and Clinical Pharmacology review was completed by Kia Jackson on November 3, 2017.

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

1. SE0004825 – SE004828 and SE0004875 – SE0004880 provides information on pH, total nicotine, and free nicotine in the surrogate products, which represent the new products, and the predicate products in your response to the Preliminary Finding letter dated September 6, 2016. The new products SE0004825 – SE004828 and SE0004875 – SE0004880 have increased free nicotine compared to the corresponding predicate products. You provide support for the weaknesses in using the Henderson-Hasselbalch Equation to determine free nicotine, but do not provide an alternative method for estimating free nicotine delivery. You also cite a 2014 Pickworth et al study, which examines amended smokeless tobacco products with pH differences greater than the differences between the surrogate for each new product and the respective predicate products. The study reveals comparable plasma nicotine levels and area under the curve values between the two high pH products, and no substantial difference in perceived product strength or preference between any products. However, due to the small sample size (n=7), descriptive statistics only were used for most variables. As such, the results from this study only qualitatively describe the features of the sample evaluated and cannot be used to represent or infer conclusions about the potential impact of the changes in free nicotine between the new and predicate products on the general population.

   Increased availability of free nicotine to the user in the new products may lead to increased levels of nicotine dependence among users. Provide adequate evidence that these changes in free nicotine between the new and predicate products do not cause the new products to raise different questions of public health. Such evidence could include a clinical pharmacokinetic study to determine systemic nicotine exposure following use of the surrogate and predicate products, and corresponding subjective measures to assess abuse liability. However, there may be other ways of addressing this deficiency.

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

As TPL, I disagree that the above deficiency should be conveyed to the applicant. As discussed above in section 4.1, I have concluded that the calculated free nicotine content does not sufficiently take into account the dissolution data, and relevant information from the study published by Pickworth, et al. (2014), and therefore such calculated increases in free nicotine do not cause the new tobacco products to raise different questions of public health. In short, I disagree with the Behavioral and Clinical Pharmacology reviewer's conclusion that human pharmokinetics data are necessary to demonstrate that free nicotine increases do not alter the addictive properties of the new tobacco products compared to corresponding predicate tobacco product. The Behavioral and Clinical Pharmacology reviewer based that determination on the evaluation of the change in calculated free nicotine between the new and predicate tobacco products. However, this difference was calculated using the Henderson-Hasselbalch equation, which can provide an inflated measurement of total free nicotine content. Instead, the dissolution profiles provide a better estimate of free nicotine release rates and content than the Henderson-Hasselbalch equation. As TPL, I find that the applicant's dissolution data, and the Pickworth study are sufficient evidence to demonstrate that there is not a statistically significant increase in free nicotine in the new tobacco products. Therefore, the deficiency identified in the Behavioral and Clinical Pharmacology review regarding the free nicotine differences between the new and predicate products, should not be conveyed to the applicant, because I conclude that the apparent free nicotine increases do not cause the new tobacco products to raise different questions of public health. Therefore, the differences in characteristics related to consumer use of the product and impact on exposure and behavior between the new tobacco products and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health.

5. ENVIRONMENTAL DECISION

An environmental review was completed by Shannon Hanna on May 5, 2019.

The final environmental review found a lack information on the environmental effects of manufacturing the new tobacco products, a lack evidence that the manufacturing facility is in compliance with relevant federal, state, and local environmental regulations, a lack information on the first- and fifth-year projected market volumes of the new tobacco products, a lack information regarding the marketing status of the predicate tobacco products, a lack information about the environmental effects of disposal of the new tobacco products, and a lack of evidence for compliance with the Endangered Species Act (ESA) and the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES).. Therefore, additional information is needed to determine whether to prepare an Environmental Impact Statement (EIS) or Finding of No Significant Impact (FONSI).

6. CONCLUSION AND RECOMMENDATION

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

- Increased free nicotine concentrations (b) (4) in all new tobacco products
- Ingredient differences in pH modifiers such as (b) (4), and (b) (4)

- Addition of menthol in SE0004877 and increase in menthol of 255% in SE0004826 due to the addition of the ingredient - (b) (4)
- Different container closure system: plastic can with a metal lid instead of a plastic can with a plastic lid
- A metal lid coated with Gold R/C enamel is used in the new tobacco product instead of a plastic lid used in the predicate tobacco product
- Addition of the preservative (b) (4)
- Different flavoring ingredients in the new tobacco products for SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880
- Overall tobacco amounts decreased by 3-37 mg/g (0.9 – 10.3%)
- (b) (4) leaf increased by (b) (4) whereas (b) (4) decreased by between (b) (4) and (b) (4) leaf increased by up to (b) (4)
- Decrease in total TSNAs, NNN, and NNK ranging from 6% - 45%

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco products to raise different questions of public health. The applicant has sufficiently characterized the tobacco blends and ingredients added to tobacco between the new and predicate tobacco products. There were only minor differences in the tobacco blends between the new and predicate tobacco products; these differences do not cause the new tobacco product to raise different questions of public health. In all new tobacco products, the higher pH ranges result in higher free nicotine concentrations of 18 – 88% (3.19 – 4.85 mg). Additionally, there were ingredient differences in pH modifiers such as (b) (4) that could have an influence on the pH between the new and predicate tobacco products. However, as discussed above this change in pH and free nicotine does not cause the new tobacco products to raise different questions of public health. While it was noted that the new tobacco products have higher free-nicotine levels compared to the corresponding predicate tobacco products, the applicant provided adequate information to assess the dissolution study provided to determine if these differences cause the new tobacco products to raise different questions of public health. In addition, the tobacco cut size of the new and predicate tobacco products was not provided. However, for SE0004825, SE0004827, SE0004829, SE0004875, SE0004876, and SE0004878, the applicant adequately demonstrated that it is unlikely that any difference would exist between the tobacco cut size of the new and corresponding predicate tobacco products as the tobacco cutting parameters used to manufacture the new and corresponding predicate tobacco products are identical. For SE0004826, SE0004828, SE0004877, SE0004879, and SE0004880, the evaluation of HPHCs showed that many HPHCs decreased between the new and predicate tobacco products and thus, any changes in the tobacco cut size was unlikely in this case, to influence constituent yields of the new tobacco products by altering the constituent dissolution rates. Furthermore, for SE0004877 and SE0004826, notable increases in menthol (in the form of (b) (4), which has been shown to enhance the permeability of buccal and esophageal tissues and would therefore be expected to cause increased exposure to toxicants present in smokeless tobacco products, were noted between the new and predicate tobacco products; however, the applicant provided evidence including demonstrating a decrease in NNN and NNK between the new and predicate tobacco products, and therefore, in this case, these increases in menthol do not cause the new tobacco products to raise different questions of public health. Additionally, there is a container closure system change in the lid material of the plastic can between the new and predicate tobacco products; a metal lid is used in the new tobacco product compared to a plastic lid in the predicate tobacco product. Stability testing demonstrated that the

change in the lid material did not affect the stability of the new tobacco products compared to the corresponding predicate tobacco products. The applicant also provided sufficient information to demonstrate that the addition of the preservative (b) (4) in the new tobacco products compared to the corresponding predicate tobacco products do not cause the new tobacco product to raise different questions of public health. The estimated daily intake of (b) (4) in the new tobacco products do not cause the new tobacco products to raise different questions of public health when compared to the corresponding predicate tobacco products. Therefore, the differences in characteristics between the new and corresponding predicate products do not cause the new tobacco products to raise different questions of public health.

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

The new tobacco products are currently in compliance with the FD&C Act. In addition, microbiology, toxicology, and social science scientific reviews conclude that the differences between the new and corresponding predicate tobacco products are such that the new tobacco products do not raise different questions of public health. I concur with these reviews. However, the chemistry, engineering, and behavioral and clinical pharmacology scientific reviews conclude that the differences between the new and corresponding predicate tobacco products are such that the new tobacco products raise different questions of public health. I do not concur with these reviews. Briefly, I disagree with the chemistry assessment that the surrogate tobacco products are not acceptable as discussed above, as well as I disagree that the dissolution studies along with the measured pH and calculated free nicotine is not sufficient to determine that the differences in product composition do not cause the new tobacco products to raise different questions of public health. Additionally, I disagree with the engineering assessment that the applicant did not provide sufficient information regarding the product design between the new and predicate tobacco products as discussed above. Finally, I disagree with the behavioral and clinical pharmacology review that there are differences in characteristics related to consumer use of the product and impact on exposure and behavior between the new tobacco products and corresponding predicate tobacco products. The Behavioral and Clinical Pharmacology reviewer's conclusion that human pharmokinetics data are necessary to demonstrate that free nicotine increases do not alter the addictive properties of the new tobacco products compared to corresponding predicate tobacco product. The Behavioral and Clinical Pharmacology reviewer based that determination on the evaluation of the change in calculated free nicotine between the new and predicate tobacco products. However, this difference was calculated using the Henderson-Hasselbalch equation, which can provide an inflated measurement of total free nicotine content. Instead, the dissolution profiles provide a better estimate of free nicotine release rates and content than the Henderson-Hasselbalch equation and as noted above, as TPL, I find that analysis of the applicant's dissolution data, and the Pickworth study are sufficient evidence to demonstrate that there is not a statistically significant increase in free nicotine in the new tobacco products. Therefore, as TPL, I recommend that SE order letters be issued.

FDA examined the environmental effects of finding these new tobacco products substantially equivalent and found additional information is necessary to determine the impact of the action. Without this information, FDA is precluded from issuing an SE order.

An Advice/Information Request letter should be issued requesting the following information:

1. All of your SE Reports lack information on the environmental effects of manufacturing the new products. This information is used to assess the environmental impact of marketing of the new products. To address the potential effects of manufacturing, provide answers to the following:
    a. Will there be increased manufacturing due to the new products? If so, will that require additional resources for manufacturing waste disposal, such as on-site solid or hazardous waste accumulation capacity, new or expanded landfills, recycling centers, or other waste disposal or handling capacity? If these additional resources would be required, describe the environmental effects.
    b. Will manufacturing the new products result in an expansion of the manufacturing facility? If so, identify and evaluate any potential environmental impacts due to the expansion.
    c. Will there be new compounds emitted or increased amounts of compounds currently emitted from manufacturing the new products? If so, list the compounds and describe the environmental effects of those new compounds being emitted.
    d. Will manufacturing the new products lead to changes in air emissions or wastewater discharges from increased manufacturing? Will a revised or new air emissions or wastewater discharge permit be required?
    e. Will manufacturing the new products require any additional environmental controls? If yes, what are these controls and describe the environmental effects of these controls?

2. All of your SE Reports lack evidence that the manufacturing facility is in compliance with relevant federal, state, and local environmental regulations. The significance of environmental impacts (and thus the justification for a finding of no significant impact) is in part indicated by whether the action may violate federal, state, or local law or requirements imposed for the protection of the environment (40 CFR 1508.27(b)(10)). If applicable, provide a statement that you comply with relevant federal, state, and local environmental regulations. Otherwise, discuss potential violations of any federal, state, and local environmental regulations and your mitigation to comply with the regulations.

3. All of your SE Reports lack information on the first- and fifth-year projected market volumes of the new products. Marketing information is used to quantitatively assess the environmental impacts of manufacturing, use, and disposal of the new products. In Table 1, provide the projected market volumes of the new products. Note any information you deem confidential so that it can be placed in a confidential appendix to the public EA document.

Table 1			
STN	Measure	First-Year Market Volume	Fifth-Year Market Volume
SE0004825	Cans		
SE0004826	Cans		
SE0004827	Cans		
SE0004828	Cans		
SE0004829	Cans		
SE0004875	Cans		
SE0004876	Cans		
SE0004877	Cans		

SE0004878	Cans		
SE0004879	Cans		
SE0004880	Cans		

4. All of your SE Reports lack information regarding the marketing status of the predicate products. Marketing information is used to quantitatively assess the environmental impacts of manufacturing, use, and disposal of the new products as compared to the predicate products. Provide the following information:
   a. Specify clearly whether or not the predicate products are currently marketed.
   b. If the predicate products are currently marketed, is it intended that they will be simultaneously marketed with the new products after receiving marketing orders? If not currently marketed, provide a statement that they are not intended to be simultaneously marketed with the new products.
   c. If the predicate products are to be marketed simultaneously with the new products, provide the first- and fifth-year market projections for the predicate products in Table 2.

Table 2

STN	Measure	First-Year Market Volume	Fifth-Year Market Volume
Predicate product to SE0004825	Cans		
Predicate product to SE0004826	Cans		
Predicate product to SE0004827	Cans		
Predicate product to SE0004828	Cans		
Predicate product to SE0004829	Cans		
Predicate product to SE0004875	Cans		
Predicate product to SE0004876	Cans		
Predicate product to SE0004877	Cans		
Predicate product to SE0004878	Cans		
Predicate product to SE0004879	Cans		
Predicate product to SE0004880	Cans		

5. All of your SE Reports lack information about the environmental effects of disposal of the new products. This information is used to assess the environmental impact of marketing the new products. To address the potential effects of disposal, provide answers to the following questions:

a. Will disposal of the new products require additional resources (e.g., new landfills, recycling centers) for waste disposal? If so, describe the environmental effects of these increased resources.
b. Will there be new compounds emitted or increased amounts of currently emitted compounds from the disposal of the new products? If so, list the compounds and describe the environmental effects of those new compounds being emitted.

6. All of your SE Reports lack evidence that you are in compliance with the Endangered Species Act (ESA) and the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). All federal actions are required to comply with ESA and CITES, therefore FDA evaluates the potential for violations of ESA and CITES due to its proposed product authorization actions. To assess if any adverse effects are anticipated from the proposed actions, provide a discussion of any adverse effects, if applicable, on any endangered species or the critical habitat of the species identified under ESA and CITES due to (i) the materials or ingredients used to manufacture the new products, (ii) the manufacturing process itself, and (iii) the disposal of the new products.

If the applicant adequately responds to the request and an EIS or FONSI is completed, SE order letters should be issued for the new tobacco products in SE0004825 - SE0004829 and SE0004875 - SE0004880, as identified on the cover page of this review.