FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0012626 and SE0012633

SE0012626: Copenhagen Bold Wintergreen Flavor Packs (1.55g)	
Package Type	Plastic Can with Metal Lid
Portion Count	15
Package Quantity	23.25 g
Portion Mass	1550 mg
Portion Length	27.4 mm
Portion Width	20.9 mm
Portion Thickness	4.3 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Wintergreen
Additional Property	(b) (4)
SE0012633: Copenhagen Bold Wintergreen Flavor Packs (2.0g)	
Package Type	Plastic Can with Metal Lid
Portion Count	12
Package Quantity	24.0 g
Portion Mass	2000 mg
Portion Length	31.4 mm
Portion Width	23.4 mm
Portion Thickness	4.6 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Wintergreen
Additional Property	(b) (4)
Common Attributes of SE Reports	
Applicant	U.S. Smokeless Tobacco Company
Report Type	Regular
Product Category	Smokeless Tobacco Product
Product Sub-Category	Portioned Moist Snuff
Recommendation	
Issue Substantially Equivalent (SE) orders.	

Technical Project Lead (TPL):

Todd L. Cecil -S
Digitally signed by Todd L. Cecil -S
Date: 2018.06.05 15:23:32 -04'00'

Todd L. Cecil, Ph.D.
DPS Associate 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: 2018.06.05 16:53:40 -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:

SE0012626: Copenhagen Bold Wintergreen Flavor Packs (1.55g)	
Product Name	Skoal Pouches Wintergreen
Package Type	Plastic Can with Metal Lid
Portion Count	15
Package Quantity	23.25 g
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Portion Thickness	4.3 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Wintergreen
Additional Property	(b) (4)
SE0012633: Copenhagen Bold Wintergreen Flavor Packs (2.0g)	
Product Name	Skoal Pouches Wintergreen
Package Type	Plastic Can with Metal Lid
Portion Count	15
Package Quantity	23.25 g
Portion Mass	1550 mg
Portion Length	40 mm
Portion Width	18 mm
Portion Thickness	4.3 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Wintergreen
Additional Property	(b) (4)

The predicate tobacco products are portioned moist snuff smokeless tobacco products manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On November 13, 2015, FDA received SE Reports from U.S. Smokeless Tobacco Company. FDA issued Acknowledgement letters to the applicant on May 23, 2016. FDA issued an Advice and Information Request (A/I) letter on November 1, 2016. FDA issued a Correction letter on November 10, 2016 to correct a deficiency in the A/I letter for SE0012626. FDA received the applicant's amendment on December 22, 2016 (SE0013794). FDA issued a Preliminary Finding letter on March 16, 2017, and FDA received the applicant's amendment on April 14, 2017

(SE0014032). FDA issued Not Substantially Equivalent (NSE) orders on July 13, 2017. On August 8, 2017, the applicant submitted a request for supervisory review ("appeal") under 21 CFR 10.75, stating that the NSE orders should be overturned. CTP denied the appeal on January 2, 2018. Subsequently, on February 2, 2018, the applicant filed a complaint for declaratory and injunctive relief in the United States District Court for the District of Columbia, requesting, among other things, that the Court vacate and set aside the NSE orders and the appeal decision. Upon review of the administrative record, FDA found that there was relevant information that was not adequately assessed. As a result, FDA issued "Rescission of Not Substantially Equivalent Order" letters on March 26, 2018, and started a new cycle of review. On April 13, 2018, FDA spoke to the applicant to clarify information submitted by the applicant in the final amendment preceding the NSE orders (SE0014032). FDA received the requested information in an amendment on April 23, 2018 (SE0014643). On May 4, 2018, FDA spoke to the applicant to request environmental information. FDA received the applicant's amendment on May 11, 2018 (SE0014718).

Product Name	SE Report	Amendments
Copenhagen Bold Wintergreen Flavor Packs (1.55g)	SE0012626	SE0013794 SE0014032 SE0014643 SE0014718
Copenhagen Bold Wintergreen Flavor Packs (2.0g)	SE0012633	

1.3. SCOPE OF REVIEW

A TPL review by Kenneth Taylor on July 21, 2017, concluded that the applicant failed to demonstrate that the differences in characteristics between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. Upon review of the administrative record, FDA found that there was relevant information that was not adequately assessed. This review captures all regulatory, compliance, and scientific reviews completed for these SE Reports prior to the NSE-order and the regulatory, compliance, and scientific reviews completed subsequent to the receipt of SE0014718.

2. REGULATORY REVIEW

Regulatory reviews were completed by Angela Brown on May 23, 2016.

The final reviews conclude that the SE Reports are administratively complete.

3. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews to determine whether the applicant established that the predicate tobacco products 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 dated July 21, 2016, concluded that the evidence submitted by the applicant was adequate to demonstrate that the predicate tobacco products are grandfathered and, therefore, are eligible predicate tobacco products. The applicant subsequently removed one of the eligible predicate tobacco products, leaving a single eligible predicate tobacco product for both of the new 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 May 24, 2018 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

Chemistry reviews were completed by Matthew Hassink on July 13, 2016, Melissa McCulloch on February 3, 2017 and corrected on March 10, 2017, An Vu on May 30, 2017, and Lida Oum on June 5, 2018.

The final chemistry review concludes that the new tobacco products have different characteristics related to product chemistry 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:

- Higher (b) (4) [redacted]
- Higher B[a]P yield (SE0012633 only)
- Higher amounts of (b) (4) [redacted]
- Higher amounts of (b) (4) [redacted]
- Higher level of target pH
- Higher amount of calculated free nicotine per portion
- Higher amount of total nicotine per portion (SE0012633 only)
- Higher amount of tobacco per pouch (SE0012633 only)
- Different pouch material (b) (4) [redacted] in the predicate products

The higher amount of (b) (4) [redacted] may result in an increase in particulate-borne harmful and potentially harmful constituents (HPHCs) like B[a]P and soil-sourced HPHCs like cadmium and arsenic, while the lower amount of (b) (4) [redacted] may lead to a decrease in B[a]P. The applicant provided HPHC measurements for B[a]P, cadmium, arsenic, NNN, and NNK. The results show that all HPHC measurements, except for B[a]P in SE0012633, were the same or lower in the new tobacco products when compared to the predicate tobacco product. The role of a chemistry review is to determine whether chemical measurements were conducted in an appropriate manner and to determine whether differences in the new and predicate tobacco products result in statistically different amounts of HPHCs to which a user would be exposed. The finding of higher B[a]P yield in the new tobacco product of SE0012633 was statistically non-equivalent to the result of the predicate tobacco product. The evaluation of whether the impact of this change in the HPHC value upon the user would cause the new product to raise different questions of public health was deferred to toxicology for further evaluation. Higher amounts of (b) (4) [redacted] and (b) (4) [redacted] in the new tobacco

products were also deferred to toxicology for further evaluation. The higher amounts of pH modifiers (b) (4)), the change in target pH, and the higher amount of calculated free nicotine in the new products are related[1]. Thus, a finding that the free nicotine increase does not raise different questions of public health would also indicate that the changes in pH and changes in the pH modifiers similarly do not raise different questions of public health from a chemistry perspective. As indicated above, the chemist's responsibility is to evaluate any change to the tobacco products and their affects upon the HPHCs released by the new and predicate products. The chemist deferred the decision of whether changes in pH and portion size which led to a calculated increase of free nicotine per portion and the measured increase in total nicotine per portion (SE0012633 only) in the new tobacco products to the Behavioral and Clinical Pharmacology (BCP) branch for further evaluation of the effects of these changes on the user. The change in the total tobacco per portion may be one of the causes of the increase in total nicotine and may have also been responsible for increases in B[a]P. Each of these findings have been deferred as described above.

The change in the pouch material may result in different nicotine release characteristics, which may lead to changes in use patterns or initiation. The new and the predicate tobacco products are both portioned. To demonstrate that the differences in the pouch material do not affect the nicotine release characteristics, the applicant provided dissolution profiles of the new and predicate tobacco products, which indicate that the release rates are statistically equivalent. Prior to the July 13, 2017 NSE orders, review of the dissolution data was completed by the engineering reviewer rather than the chemistry reviewer. While the 3rd engineering review raised relevant issues, it did not account for chemistry considerations, and resulted in the issuance of engineering deficiencies in the NSE letter. Specifically, the engineering review stated that the use of the methodology described in a CDER guidance[2] on dissolution testing did not apply to tobacco products. Instead, with respect to nicotine dissolution release rates, the 3rd engineering review focused on the differences in release rates between the new and predicate products at early time points. While the engineering review correctly noted that nicotine release rates during the first several minutes of use are important, differences in dissolution profiles over the entire time period, including the first several minutes, are encompassed in the methodology described in the guidance, which represents the best current thinking on the comparison of dissolution profiles. Because dissolution is a chemical measurement, dissolution profiles are properly evaluated by the chemistry reviewer. From the chemistry perspective, the focus of comparison of two dissolution profiles is on the initial 4-6 timepoints[3], which roughly equate to the time period encompassing the rate of the initial rise in Pharmacokinetic (PK) studies of nicotine absorption. These timepoints are used to calculate the difference factor f_1

[1] In the simplest case, a change in the relative amounts of the acidic (i.e., (b) (4)), basic (i.e., (b) (4)), and counter ion (i.e., (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.

[2] FDA, Guidance for Industry (1997): Dissolution Testing of Immediate Release Solid Oral Dosage Forms. **1997**.

[3] 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 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 products evaluated the initial timepoints that comprise the fastest changing portions of the products' respective dissolution curves.

and similarity factor, f_2[4]. 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. The applicant provided two different dissolution data sets prior to the NSE findings. At that time, FDA had not received information about which of the data sets were intended for our evaluation, i.e., that the second data set was meant to replace/supercede the first. When evaluating the similarity factor, the chemistry reviewer evaluated both of the data sets together and found that the similarity factor fell below the acceptance range for statistical equivalence. However, if the second dataset, provided in the April 14, 2017 amendment (which is a more complete data set as it contained additional replicates) is evaluated in isolation, the similarity factor falls within the acceptance range. In the April 23, 2018 amendment, the applicant stated that the data set provided in the April 14, 2017 amendment was intended to replace the data set initially provided. The applicant explained that the second data set contained new and predicate tobacco products that have similar manufacture dates and were tested using the same laboratory and approximately at the same time in order to minimize random and systematic error for the evaluation. The first data set included new product data that was collected about a year prior to the predicate product data which introduces method bias to the comparison that is not present in the second data set. The first data set also included only 7 replicates while the second set included 12 replicates. A larger set of replicates for each of the new and predicate product is necessary in order to use an f1/f2 analysis. The applicant's rationale for replacing the initial data set is acceptable from a chemistry perspective. Accordingly, based on the second dissolution data set, the nicotine release rates for the new and predicate tobacco products are considered equivalent.

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 chemistry perspective.

4.2. ENGINEERING

Engineering reviews were completed by James Cheng on August 1, 2016, February 6, 2017, May 25, 2017, and June 4, 2018.

The final engineering review concludes that the new tobacco products have different characteristics related to product engineering 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:

- Increased pouch material air permeability
- Higher pouch material basis weight
- Increased tobacco filler mass (SE0012633 Only)
- Increase in tobacco cut size

[4] FDA, Guidance for Industry (1997): Dissolution Testing of Immediate Release Solid Oral Dosage Forms. **1997**.

The new tobacco products use a different pouch material than the predicate tobacco products. The new tobacco product pouch material demonstrates a higher air permeability and pouch material basis weight. Increases in air permeability and pouch material basis weights may lead to an increase in the nicotine release rates of the new tobacco products. Changes in the release rate are noted in both of the datasets provided by the applicant. As discussed above, although two sets of data were provided by the applicant, the applicant clarified that the second set of data provided in April 2017 was the correct information to consider in review. The possible increases in nicotine release rates based on the differences in air permeability and pouch material basis weights were addressed in the latest cycle of review because the chemistry review determined that the second set of dissolution release rate data provided by the applicant shows that the release rate profiles of the new and predicate products are not statistically different.

In addition, the applicant indicated that the new product tobacco filler was manufactured using a larger cut size than the predicate tobacco product. Larger particle size may lead to a decrease in the nicotine release rate. The evaluation of the changes in release rate were deferred to the chemistry reviewer. However, the applicant provided dissolution release rate data comparing the loose tobacco of the new and predicate products that show that the loose tobacco filler of both products have similar release profiles. This was found acceptable in the February 2017 engineering review and that conclusion has not changed.

In SE0012633, that applicant states that the new tobacco product contains more tobacco filler than the predicate tobacco product. An increase in tobacco filler mass may lead to an increase in total nicotine and other HPHCs. The evaluation of a potential increase in nicotine and other HPHCs due to the increased amount of tobacco filler per pouch was deferred to social science in the July 2016 engineering review.

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 an engineering perspective.

4.3. MICROBIOLOGY

A microbiology review was completed by Prashanthi Mulinti on January 27, 2017.

The final microbiology review did not identify any differences in characteristics between the new and corresponding predicate tobacco products that could cause the new tobacco products to raise different questions of public health from a microbiology perspective. 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 related to product microbiology.

4.4. TOXICOLOGY

Toxicology reviews were completed by James Hobson on August 9, 2016, and by Ana S. DePina on February 24, 2017, and June 6, 2017.

The final toxicology review concludes that the new tobacco products have different characteristics related to 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:

- Increase in B[a]P (SE0012633 Only)
- Higher amounts of (b)(4) [redacted], and (b)(4) [redacted]

For SE0012633, the level of B[a]P in the new tobacco product is slightly higher than is found in the predicate tobacco product. However, this increase is estimated to cause a minimal increase in excess cancer risk and is well below the background level from diet. Additionally, there are several other carcinogenic HPHCs which are found at lower levels in the new tobacco product than in the predicate tobacco product, raising the possibility of an overall reduction in excess cancer risk. In this particular exposure scenario (new and predicate tobacco products, HPHCs in question), given the likelihood that the small increase in B[a]P will not pose toxicity concerns, this difference does not cause the new tobacco product to raise different questions of public health.

The increase in (b)(4) [redacted] may lead to increase in glycyrrhizic acid content, which could lead to adverse health effects such as hypokalemia and hypertension. However, the glycyrrhizic acid content in the new tobacco products is lower than certain food products and the JECFA recommended intake level, such that it is unlikely to cause adverse effects. In addition, the actual increase in glycyrrhizic acid in the new tobacco products as compared to the predicate tobacco product is much lower than the JECFA/EFSA recommended intake level of 100 mg/day. The preponderance of toxicological data suggests that the addition or increase of [redacted] containing ingredients here does not cause the new tobacco products to raise different questions of public health.

(b)(4) [redacted] is found in the new tobacco product at a higher level than the predicate tobacco product. This compound is GRAS in food products (21 CFR 180.37). The likely exposure to (b)(4) [redacted] from the new tobacco products is lower than the Allowable Daily Intake level. Based on this data, the increase in (b)(4) [redacted] here 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 Elisabeth Sherman on August 1, 2016, and February 10, 2017.

The final social science review concludes that the new tobacco products have different characteristics from the corresponding predicate tobacco products, but the differences do not

cause the new tobacco products to raise different questions of public health from a social science perspective. The review identified the following differences:

- Increased tobacco quantity per pouch (SE0012633 only)
- Fewer portions per package (SE0012633 only)

The study results submitted by the applicant address FDA's concerns about increased tobacco quantity per pouch related to consumer perception and use. The studies indicate that users of moist snuff are likely to select and use the new tobacco product consistent with their current portion usage and will not show increased consumption attributed to increased pouch size. Therefore, the changes in tobacco quantity per pouch of the magnitude in these products do not cause the new tobacco products to raise different questions of public health from a social science perspective. The decrease in the number of portions per package may decrease harm perceptions or reduce barriers to initiation by lowering the price of the product, and there is evidence that price influences consumer behavior related to tobacco use[5]. The applicant provided studies that indicated that customers' perception of their products[6] are not changed by the number of pouches per package. The studies submitted by the applicant address FDA's concerns that changes in portion count of this magnitude may raise different questions of public health from a social science perspective. Additionally, the Office of Science (OS) developed a memorandum[7] summarizing its current thinking on product quantity changes, which futher supports OS' determination that, at this time, changes in tobacco product quantity do not cuase the new products to raise different questions of public health. Therefore, the differences in product characteristics related to consumer perception and use do not cause the new tobacco products to raise different questions of public health.

4.6. BEHAVIORAL AND CLINICAL PHARMACOLOGY

Behavioral and clinical pharmacology (BCP) reviews were completed by Megan Schroeder on May 30, 2017 and Chad Reissig on June 5, 2018.

The final behavioral and clinical pharmacology review concludes that, based on free nicotine content, 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. However, as discussed in the Conclusion and Recommendation section of this TPL review, I conclude that the free nicotine content estimate does not sufficiently take into account the dissolution data, relevant information from a study published by Pickworth, et al. (2014), and

[5] Chaloupka, F. J., & Warner, K. E. (2000). The economics of smoking. NBER Working Paper no. 7047. Cambridge, MA: National Bureau of Economic Research.
[6] Study was conducted with comparable Altria smokeless tobacco products (comparing an 18 pouch per can product to a 15 pouch per can product).
[7] See memorandum on product quantity changes, dated December 7, 2017.

the analysis by the chemistry reviewer, and therefore such estimates of increases in free nicotine do not cause the new tobacco products to raise different questions of public health.

The BCP-review identified the following deficiency as *not* being adequately resolved:

1. Your SE Reports SE0012626 and SE0012633 and amendments provide information on the difference in free nicotine between the new and predicate products. …
   You cite data from Pickworth and colleagues (2014) that examined nicotine pharmacokinetics of several ST products with different pH levels and thus, different free nicotine content levels. However, the study was small (n=7), which limited statistical analyses to qualitative descriptions. In addition, difference in the methyl salicylate content of the products may confound comparisons across the study conditions.

   You also claim that under controlled conditions and using identical ST products, there is individual variability in nicotine extraction efficiency from smokeless tobacco products. You provide data from Study No. ALCS-RS-15-05-MST to support this assertion, and demonstrate that products with pH values similar to the new and predicate products have similar pK profiles. However, study ALCS-RS-15-05-MST compared different portion sizes of smokeless tobacco (1.55g versus 2.0g), with dissimilar product formats (loose vs. pouched) so it is unclear whether the changes in nicotine release were due to changes in pH or portion size. Because of the different formats and portions sizes, these data do not address the salient aspect of the deficiency: that the increased free nicotine in the new products may increase exposure to nicotine, and increase the abuse liability and dependence potential of the new products relative to the predicate products.

   Nicotine is the primary addictive constituent of tobacco products and like all drugs of abuse, the dose (or amount) of nicotine is directly associated with its abuse liability. The amount of free nicotine contained in an ST product is determined by total nicotine content and the pH of the product. Free nicotine content may affect nicotine exposure by more readily crossing biological membranes, including the oral mucosa. The new products have substantially increased free nicotine content per portion compared to the predicate product. The increased free nicotine content may increase nicotine exposure and dependence, increase the abuse liability of the product, alter user behaviors. These changes in behavior may result in increased use of the new products resulting in increased exposure to HPHCs. Provide scientific evidence to demonstrate that the changes in free nicotine content do not cause the new products to raise different questions of public health relating to tobacco addiction. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

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

does not sufficiently take into account the dissolution data, relevant information from the Pickworth, et al. (2014) study, and the analysis by the chemistry reviewer. Accordingly, I find that the estimates of increases in free nicotine between the new and corresponding predicate products do not cause the new tobacco products to raise different questions of public health.

5. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on June 5, 2018. The FONSI was supported by an environmental assessment prepared by FDA on June 5, 2018.

6. CONCLUSION AND RECOMMENDATION

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

- Higher [redacted]
- Higher B[a]P yield (SE0012633 only)
- Higher amounts of [redacted]
- Higher amounts of [redacted]
- Higher level of target pH
- Higher amount of calculated free nicotine per portion
- Higher amount of total nicotine per portion (SE0012633 only)
- Higher amount of tobacco filler per pouch (SE0012633 only)
- Increase in tobacco cut size
- Different pouch material [redacted]
- Increased pouch material air permeability
- Higher pouch material basis weight
- Fewer portions per package (SE0012633 only)

A TPL review by Kenneth Taylor on July 21, 2017, concluded that the applicant failed to demonstrate that these differences in characteristics do not cause the new tobacco products to raise different questions of public health. The July 2017 TPL review identified the following deficiencies to support this conclusion:

- Increased nicotine dissolution rate[8]
- Differences in pouch material[9]
- Increase free nicotine level[10]
- Surrogate predicate data is not useful in substantial equivalence determination when predicate data is available (for benzo[a]pyrene levels (SE0012633 only) and nicotine dissolution rate)[11]

[8] Deficiency 2 and 4
[9] Deficiency 3
[10] Deficiency 5
[11] Deficiency 1

Upon review of the administrative record, FDA found that there was relevant information that was not adequately assessed. Specifically, the dissolution data was evaluated by an engineering reviewer rather than the chemistry reviewer, and the engineering reviewer drew conclusions that were contradictory to the typical practice of the chemistry review standard. The result of the misinterpretation led to defiencies associated with the dissolution rate and the pouch material differences. Further, the July 2017 TPL review raised deficiencies related to surrogate product use, however, based on additional information submitted by the applicant in April 2018, I conclude that new and predicate tobacco product data were complete and appropriate to evaluate the characteristics of the new and predicate tobacco products and whether those characteristics cause the new products to raise different questions of public health.
Based on the most recent evaluations by chemistry, engineering, and BCP as well as additional information from the applicant,[12] I conclude that the applicant has demonstrated that the issues raised in the July 2017 TPL review are adequately resolved and, 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. Each of the deficiencies raised in the July 2017 TPL review are discussed further below.

Surrogate Predicate Products

Regarding the surrogate predicate tobacco products and surrogate comparator tobacco product, the applicant relied on surrogate predicate tobacco products in the second dissolution study.

The surrogate predicate product data provided by the applicant consisted of an identical product to the identified predicate tobacco product with a single change representing approximately 1% of the total tobacco content of the tobacco blend. That change was in the relative tobacco blend of the fermented tobacco added as a seed for fermentation of the tobacco blend in the manufacture of the tobacco filler. The difference in the tobacco blend is too small to cause a difference in the dissolution characteristics when compared to the predicate tobacco product. Thus, throughout the SE reviews, FDA referred to the surrogate for the predicate product or "surrogate for GF1200229" as the predicate product.

The surrogate comparator tobacco product was provided as an additional comparator for the analysis of B[a]P. However, there was sufficient data provided for the new and predicate tobacco products, such that the surrogate comparator data was not needed. The evaluation of the dissolution study discussed in this TPL review is limited to the new and predicate tobacco products. Because the dissolution data for the new and predicate tobacco products are adequate to support a finding of substantial equivalence, data for the surrogate comparator products are unnecessary, and this concern is no longer relevant.

Nicotine dissolution rate

Regarding the increased nicotine dissolution rate, the applicant submitted dissolution study results in response to the November 2016 A/I letter[13] that suggested dissolution rates were

[12] April 23, 2018, amendment (SE0014643)
[13] December 22, 2016, amendment (SE0013794)

increased for the new tobacco products compared to the corresponding predicate tobacco product. FDA included a deficiency in the March 2017 Preliminary Finding letter expressing concern with this increase in dissolution rate. In response, the applicant submitted results from a second dissolution study[14] that suggested dissolution rates were comparable between the new and corresponding predicate tobacco products. At the time, the applicant did not adequately explain why the second dissolution study results should supersede the original dissolution study results. Therefore, the July 2017 TPL review concluded that the nicotine dissolution may not be comparable between the new and corresponding predicate tobacco products.

I conclude that the April 2018 amendment provides adequate rationale that the second dissolution study results should supersede the original dissolution study results. The applicant explained that the batch of the new tobacco products used for the first dissolution study (manufactured in September 2014 and tested in December 2015) were compared to remanufactured predicate tobacco products manufactured and tested in September 2016. The new tobacco product used to provide the first data set were depleted at the time when the applicant received the Preliminary Finding letter. Therefore, to conduct additional dissolution testing in response to the Preliminary Finding letter, the applicant manufactured a second batch of new products for testing. The second dissolution testing was conducted using newly manufactured (March 2017) new products, and the same manufacturing batch (dated September 2016) of the predicate product as used for the first dissolution study. The first dissolution testing was conducted using seven replicates for each of the new and predicate product and by two different testing laboratories using different methods. Such testing may contribute to data variability and systematic bias. The testing of the second sets of dissolution data provided were conducted by the same laboratory (b) (4) [redacted]) using the same methods, which would reduce the analytical error associated with multiple laboratories testing. In addition, a larger set of replicates (12 instead of 7) for each of the new and predicate product were also used, which are necessary for the application of the f1/f2 comparison of dissolution profiles. Therefore, it is appropriate to draw conclusions from the second dissolution study submitted in response to the Preliminary Finding letter. This study demonstrates that the nicotine dissolution rates of new and corresponding predicate tobacco products are similar. Based on this study, I conclude that the dissolution rate differences between the new and corresponding products are not a concern, and the differences in characteristics that may affect dissolution rates (e.g., tobacco particle size and pouch paper material) do not cause the new tobacco products to raise different questions of public health.

Pouch material

Regarding the differences related to pouch material, the applicant relied on nicotine dissolution study results to demonstrate the differences do not cause the new products to raise different questions of public health As explained immediately above, the concerns related to the dissolution study have been adequately resolved. The dissolution results demonstrate that the pouch material differences (combined with all other differences in characteristics) do not significantly affect nicotine release rates. I conclude that the finding by the chemistry reviewer of statistically equivalent nicotine release rates adequately addresses the engineering concern of changes to the tobacco cut size and pouch materials. Therefore, I conclude that the differences

[14] April 14, 2017, amendment (SE0014032)

related to pouch material do not cause the new tobacco products to raise different questions of public health.

Free nicotine measurement

Regarding the increase in free nicotine level identified in the July 21, 2017 TPL Review, the applicant provided nicotine dissolution study results as well as literature sources including a study by Pickworth et al. The applicant also provided additional PK data in its May 11, 2018 amendment. The BCP reviewer found that the additional PK did not address the concern of increased free nicotine in the new tobacco products, leaving only the a general literature study as support for the applicant's claim. The BCP reviewer concluded that the Pickworth study is flawed, too small, and not sufficiently similar to the new and predicate tobacco products to provide conclusive evidence of a lack of change in the free nicotine at pH levels of interest to this product. The BCP reviewer concluded that the applicant had not provided adequate evidence and scientific support to demonstrate that the new tobacco products do not raise different questions of public health.

My scientific determination is that the additional PK data did not address free nicotine changes, but that there is sufficient evidence to demonstrate that these products are substantially equivalent when the evidence is viewed together for these particular products and in light of BCP's concern related to free nicotine. I base this opinion on the following evidence: 1) flaws in the weight placed on calculated free nicotine; 2) the dissolution results and the chemist's evaluation of those results; and 3) the findings of the Pickworth study. Each of these pieces of evidence are discussed more fully below:

1. The BCP reviewer states that, "The new products have substantially increased free nicotine content per portion compared to the predicate product." This statement is based solely upon the Henderson-Hasselbach Equation (HHE), which is a method for approximating the free nicotine content in a solution. The HHE equation calculates the amount of free nicotine based solely upon the solution pH and the knowledge of the dissociation constant of nicotine. The HHE calculates the amount of free nicotine present when a solution is at equilibrium, but it does not consider important confounding effects such as dynamic salivary flow, pouch material, pouch permeability, tobacco cut size, fillers and other ingredients, or the effect of transport across the oral mucosa upon the equilibrium condition. Thus, the HHE is best used as tool for the approximation of the maximum amount of free nicotine that could be present rather than an indication that all of this free nicotine is available immediately. A finding of a significant change in the free nicotine based on an HHE evaluation should be used as a *signal* that a more representative approach to estimating free nicotine is needed.

2. Here, the applicant supplied a more representative approach by submitting the results of dissolution testing. Dissolution testing measures the nicotine release in a condition that more closely resembles the human equivalent and accounts for most of the confounding differences that the HHE cannot. The results of a dissolution study provide a measure of the total nicotine released over a period of time. This specific dissolution test constantly exposes the tobacco product with fresh mediain small volume increments, which better represents the conditions of use than HHE. Dissolution testing has been used extensively in the pharmaceutical industry for the past 30 years. The

pharmaceutical industry has developed systems for measuring rate of release and for comparing the resulting dissolution profiles. The system described by the applicant and the chemistry reviewer relies upon work done by CDER and the pharmaceutical industry. Using this system, FDA has found that there is no statistically significant difference between the new and predicate tobacco products[15]. While this is a measure of the total nicotine instead of free nicotine, only nicotine in solution will dissociate to free nicotine. As described in the HHE, the nicotine to free nicotine ratio is fixed by the pH of the immediate solution; thus, the amount of free nicotine available at any given point in time is directly related to the total nicotine content. Therefore, dissolution provides the best *in-vitro* means to predict free nicotine release rates. However, these data will only provide an estimate of free nicotine and only through pharmacokinetic or pharmacodynamic measurements can free nicotine transport be definitively evaluated.

3. As indicated above, the BCP reviewer concluded that the PK data provided by the applicant did not adequately represent the new and predicate products. As also indicated above, design flaws in the Pickworth data limit the ability to draw conclusions based on the study alone. Nevertheless, it is appropriate to consider the Pickworth study in this context where the study results support analogous data sources provided by the applicant (dissolution testing), given that the characteristics of the products evaluated in the Pickworth study are very similar to the new and predicate products. Specifically, data from the Pickworth study demonstrates that there is an average initial nicotine blood level rise of approximately 20 minutes after initiation of the test, a noticeable increase in nicotine release rate at higher pH, and similar maximum nicotine blood levels at pHs similar to the new and predicate tobacco products. Similarly, an examination of the dissolution profiles provided by the applicant demonstrates a rapid rise in nicotine release over about 20 minutes and a noticeable increase in nicotine release rate at higher pH (the new tobacco product has a higher pH), which closely matches the general trends in the PK data in the Pickworth study. Thus, despite the Pickworth study's limitations, general trends in the studies' data (nicotine blood level increase timeframes, peak nicotine levels, and pH effects) provide evidence which supports the finding that the applicant's dissolution testing results are sufficient to demonstrate that there are not statistically significant increases in free nicotine between the new and predicate tobacco products. The supporting evidence provided by the applicant (dissolution curves and Pickworth study results) includes a similarity between the dissolution profiles and the PK curves in terms of release times and amounts of nicotine absorbed in the blood. Only free nicotine crosses the oral membranes and unionized nicotine in the bulk solution is not physiologically active[16,17]. Thus, all of the nicotine measured in the PK curve in the Pickworth study is effectively free nicotine (or was briefly, as it crossed the oral mucosa).

In short, I disagree with the BCP reviewer's conclusion that human PK data are necessary to demonstrate that free nicotine increases do not alter the addictive properties of the new

[15] The statements in the July 21, 2017 TPL Review and July 13, 2017 NSE letter that the FDA CDER guidance on dissolution testing was inappropriate for application to tobacco products was incorrect for the reasons discussed in section 4.1.

[16] Pickworth, W. B., Rosenberry, Z. R., Gold, W., & Koszowski, B. (2014). *Journal of Addiction Research & Therapy, 5*(3), 1000184. doi:10.4172/2155-6105.1000184.

[17] Barlow, R.B. and Hamilton, J.T. (1962). *Brit. J. Pharmacology*, 18, 543-549.

tobacco products compared to corresponding predicate tobacco product. The BCP 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 HHE, 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 HHE. I find that the applicant's dissolution data, the Pickworth study, and the analysis by the chemistry reviewer combined 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 BCP 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.

The predicate tobacco products meet statutory requirements because it was determined that 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. I concur with each of the scientific reviews cited above except for the BCP review, disagree with the BCP findings, and recommend that SE order letters be issued.

FDA examined the environmental effects of finding these new tobacco products substantially equivalent and made a finding of no significant impact.

SE ORDER LETTERS SHOULD BE ISSUED FOR THE NEW TOBACCO PRODUCTS IN SE0012626 AND SE0012633, AS IDENTIFIED ON THE COVER PAGE OF THIS REVIEW.