U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of SE Reports

New Products Subject of this Review	
Submission tracking numbers (STNs)	SE0017388,SE0017425,SE0017626,SE0017648
Common Attributes	
Submission date	August 20, 2020; August 21, 2020; and August 27, 2020
Receipt date	August 20, 2020; August 21, 2020; and August 27, 2020
Applicant	Top Tobacco, LP
Product manufacturer	Top Tobacco, LP
Application type	Regular
Product category	Pipe Tobacco Products
Product subcategory	Pipe Tobacco Filler
Cross-Referenced Submissions	
All STNs	(b)(4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	
Recommendation	
Issue Substantially Equivalent (SE) orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

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Date: 2021.06.04 14:14:48 -04'00'

Kenneth M. Taylor, Ph.D.
Chemistry Branch Chief, Division of Product Science
Office of Science

Signatory Decision:

Concur with TPL recommendation and basis of recommendation

Digitally signed by Todd L. Cecil -S
Date: 2021.06.04 14:22:07 -04'00'

Todd L. Cecil, Ph.D.
Deputy Director
Office of Science

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1. BACKGROUND

1.1. NEW AND PREDICATE PRODUCTS

The applicant submitted information for the new and predicate products listed in detail in the Appendix.

1.2. REGULATORY ACTIVITY

See Appendix for products and amendments.

1.3. SCOPE OF REVIEW

This review captures all compliance, regulatory, and scientific reviews completed for the new products that are the subject of this review.

Table 1. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Regulatory	Fredris Wiley	9/2/2020; 9/4/2020	N/A	N/A
Chemistry	Ruth Ganunis	10/30/2020	Ruth Ganunis	4/2/2021
Engineering	James Melchiors	10/23/2020	N/A	N/A
Toxicology	Tameka Phillips	10/28/2020	N/A	N/A
Microbiology	Kristy HuynhNgo	10/29/2020	N/A	N/A
Environmental Science	Vyomesh Patel	10/19/2020	Vyomesh Patel	4/23/2021

2. COMPLIANCE REVIEW

The Office of Compliance and Enforcement (OCE) completed reviews to determine whether the applicant established that the predicate products are grandfathered products (i.e., were commercially marketed in the United States as of February 15, 2007). The OCE reviews dated September 30, 2020, conclude that the evidence submitted by the applicant is adequate to demonstrate that the predicate products are grandfathered and, therefore, are eligible predicate 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 April 7, 2021, concludes that the new tobacco products are in compliance with the FD&C Act.

3. SCIENTIFIC REVIEW

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

3.1. CHEMISTRY

The final chemistry review concludes that the new products have different characteristics compared to the corresponding predicate products, but the differences do not cause the new products to raise different questions of public health from a chemistry perspective.

For all SEs there are multiple changes in tobacco and non-tobacco ingredients in the filler, as discussed in chemistry review 1. In summary, for SE0017388, SE0017425, and SE0017626, there is an addition of (b) mg/g of (b)(4) a decrease of (b) mg/g of cigar tobacco (↓0.2%), and an increase of (b) mg/g of (b)(4) (↑10%), which results in an overall increase of (b) mg/g (↑5%) of total tobacco in the filler. While specific changes in the non-tobacco ingredients are further discussed below, overall there is a decrease of (b) mg/g of non-tobacco ingredients in the filler. The package quantity of the filler remains unchanged between the new and corresponding predicate tobacco products (16 oz). For SE0017648, there is a decrease of (b) mg/g (↓11%) of cigar tobacco and an increase of (b)(4) mg/g of (b)(4) (b)(4) (↑150%), which results in an overall increase of (b) mg/g (↑3%) of total tobacco in the filler. While specific changes in the non-tobacco ingredients are further discussed below, overall there is a decrease of (b) mg/g of non-tobacco ingredients in the filler. The package quantity of the filler remains unchanged between the new and corresponding predicate tobacco products (6 oz).

For SE0017388, SE0017425, and SE0017626, the new tobacco products contain (b) mg/g of (b)(4) while the corresponding predicate tobacco products do not. (b)(4) (b)(4) contains increased levels of tobacco-specific nitrosamines like NNN and NNK. The applicant provided NNN and NNK filler quantities. Since the addition of (b)(4) to the new tobacco products results in analytically equivalent or decreased quantities of NNN and NNK, the addition of (b)(4) to the new tobacco products does not cause the new tobacco products to raise different questions of public health.

For SE0017388, SE0017425, and SE0017626, the new tobacco products contain higher quantities of bright tobacco (↑10%,↑ (b) mg/g) than the corresponding predicate tobacco products. However, this increase is minor (↑0.8% relative to total tobacco) and is not expected to result in measurable B[a]P smoke yield differences, and therefore does not cause the new tobacco products to raise different questions of public health. The new tobacco product in SE0017648 contains a higher quantity of (b)(4) (↑150%,↑ (b)(4) mg/g) compared to the corresponding predicate tobacco product. The applicant did not provide B[a]P filler data. A deficiency was sent to the applicant to provide tobacco filler quantities of B[a]P for the new and corresponding predicate tobacco products. In this amendment the applicant provided filler data which showed B[a]P levels are analytically equivalent between the new and corresponding predicate tobacco products, and therefore, the increase in (b)(4) does not cause the new tobacco products to raise different questions of public health.

In all SE reports the new tobacco products contain a higher (↑3-5%) total quantity of tobacco in the filler compared to the corresponding predicate tobacco products, which may impact HPHC data. In addition, the filler has changes in tobacco types, individual tobacco quantities and non-tobacco ingredients in new tobacco products compared to the corresponding predicate tobacco products, which may also impact HPHC data. A deficiency was sent to the applicant to provide scientific evidence and rationale why these increases in total tobacco do not cause the new tobacco products to raise different questions of public health. In response to the deficiency, the applicant referenced nicotine, arsenic, cadmium, NNN, and NNK filler quantities in the original SE reports, which were also discussed in chemistry review cycle 1. Since the same portion of tobacco filler of the new and corresponding predicate tobacco products was tested, the data indicates that the new tobacco products overall have analytically equivalent or decreased HPHC

levels in comparison to the corresponding predicate tobacco products (see Table 2 ofthe Chemistry review). That the 3-5% higher total tobacco in the new tobacco products does not result in higher HPHC quantities in the new tobacco products may be attributed to changes in tobacco types, individual tobacco quantities and non-tobacco ingredients but is difficult to be attributed to specific changes of a tobacco type, a particular tobacco quantity or an ingredient. Therefore, the change in total quantity of tobacco does not cause the new tobacco product to raise different questions of public health.

The new tobacco products contain higher quantities of (b)(4), ↑34% (↑(b) mg/g) in SE0017388, SE0017425, and SE0017626 and ↑32% (↑(b) mg/g) in SE0017648. In addition, (b)(4) is present in the new tobacco products in SE0017388, SE0017425, and SE0017626 at 1 mg/g and is not present in the corresponding predicate tobacco products. The largest single ingredient in (b)(4) is (b)(4) (b) mg/g). However, the impact of these higher quantities of (b)(4) are offset by lower quantities of (b)(4) in the new tobacco products, ↓47% (↓(b) mg/g) in SE0017388, SE0017425, and SE0017626 and ↓48% (↓(b) mg/g) in SE0017648 (b)(4) and (b)(4) primarily generate the same classes of compounds, such as carbonyls. An overall decrease in the combined quantities of (b)(4) and (b)(4) is expected to result in lower HPHC smoke yields of carbonyls, and therefore the changes in (b)(4) and (b)(4) do not cause the new tobacco products to raise different questions of public health.

The new tobacco products contain lower quantities of invert sugar, ↓47% (↓(b) mg/g) in SE0017388, SE0017425, SE0017626, and ↓48% (↓2(b) mg/g) in SE0017648, which corresponds to a 3.2% decrease relative to the tobacco filler weight. This difference is less than 5% and therefore is not expected to result in measurable smoke yield differences or cause the new tobacco products to raise different questions of public health. The new tobacco products contain higher quantities of potassium sorbate, ↑31% (↑(b) mg/g) in SE0017388, SE0017425, SE0017626, and ↑29% (↑(b) mg/g) in SE0017648. An increase of this small quantity, which corresponds to ↑0.032% relative to total product weight, is not expected to have an impact on HPHC smoke yields. Cocoa is present in the new tobacco products, ↑(b) mg/g in SE0017388, SE0017425, SE0017626 and ↑(b) mg/g in SE0017648, and is not present in the corresponding predicate tobacco products. The addition of this small quantity (↑0.2-0.6% relative to the total tobacco) of (b) to the new tobacco product is not expected to result in measurable smoke yield differences.

As discussed above, the applicant provided the quantities of nicotine, NNN, NNK, arsenic, cadmium, and ammonia in the tobacco filler for all SE Reports. All HPHC filler quantities are analytically equivalent or are analytically nonequivalent but decrease between the new and corresponding predicate tobacco products. Therefore, the reported HPHC filler data do not cause the new tobacco products to raise different questions of public health.
The zipper bag container closure systems for the new and corresponding predicate tobacco products in all SE Reports are identical in composition. The package quantity for the new and corresponding predicate tobacco products are identical.

Therefore, the differences in characteristics between the new and corresponding predicate products do not cause the new products to raise different questions of public health from a chemistry perspective.

3.2. ENGINEERING

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

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

3.3. MICROBIOLOGY

The final microbiology review concludes that the new products have different characteristics compared to the corresponding predicate products, but the differences do not cause the new products to raise different questions of public health from a microbiology perspective.

For SE0017388, SE0017425, SE0017626, there was a 47% decrease in (b)(4), 34% increase in (b)(4), 23% decrease in (b) (all humectants), and 31% increase in (b)(4) (b)(4) (preservative) when compared to the corresponding predicate tobacco products. For SE0017648, there was a 48% decrease in (b)(4), 32% increase in (b)(4), 2% increase in (b) (all humectants), and 29% increase in (b)(4) (preservative) when compared to the predicate tobacco product. The applicant showed that the new tobacco products have lower (7%) moisture content {oven volatiles [% OV]) compared to the predicate tobacco products. The applicant also provided finished product data for NNN and NNK levels. For all SE Reports, new tobacco products were lower for NNN (12-15%) and NNK (18- 21%). Based on the absence of fermented tobacco, % OV changes (≤11%) and NNN and NNK variations (≤21%) of the new tobacco products when compared to the predicate tobacco products, the differences in humectants and preservatives between the new and predicate tobacco products and the lack of supporting product stability data do not 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 products do not cause the new products to raise different questions of public health from a microbiology perspective.

3.4. TOXICOLOGY

The final toxicology review concludes that the new products have different characteristics compared to the corresponding predicate products, but the differences do not cause the new products to raise different questions of public health from a toxicology perspective.

The ingredients in the new and corresponding predicate tobacco products are identical except for increased quantities of (b)(4) potassium sorbate, and water. Additionally, (b) (b)(4) were added in the new tobacco products compared to the corresponding predicate tobacco products. As a result of estimated burning temperatures that do not yield additional degradation products, HPHC offsetting due to decreases in (b)(4) or low ingredient levels, these ingredient changes do not

cause the new tobacco product to raise different questions of public health from a toxicology perspective.

The applicant reported arsenic, ammonia, cadmium, NNN, and NNK levels in the tobacco filler for all the new and predicate tobacco products. The data for arsenic, ammonia, and cadmium are analytically equivalent by TOST analysis and are not considered to be different between the new and corresponding predicate tobacco products. The levels of NNK or NNN were considered analytically non-equivalent between the new and predicate tobacco products; however, the levels were decreased in the new tobacco products compared to the corresponding predicate tobacco products. Therefore, there are no toxicological concerns with the applicant-reported HPHCs in the new tobacco products.

Therefore, the differences in characteristics between the new and corresponding predicate products do not cause the new products to raise different questions of public health from a toxicology perspective.

4. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Luis Valerio, Ph.D. on April 26, 2021. The FONSI was supported by an environmental assessment prepared by FDA on April 26, 2021.

5. CONCLUSION AND RECOMMENDATION

The new products have the following differences compared to the corresponding predicate products:

- **SE0017388**
  - 5% increase in total tobacco
  - Addition of (b) mg/g (b)(4)
  - Addition of (b) mg/g (b)(4)
  - 47% decrease in (b)(4)
  - 47% decrease in (b)(4)
  - 34% increase in (b)(4)
  - 31% increase in (b)(4)
  - 23% decrease in (b)(4)
  - Addition of (b)(4)

- **SE0017425**
  - 5% increase in total tobacco
  - Addition of (b) mg/g (b)(4)
  - 10% increase in (b)(4)
  - Addition of 4.83 mg/g (b)(4)
  - 47% decrease in (b)(4)
  - 47% decrease in (b)(4)
  - 34% increase in (b)(4)
  - 31% increase in (b)(4)
  - 23% decrease in (b)(4)
  - Addition of (b)(4)

- **SE0017626**
  - 5% increase in total tobacco
  - (b)(4) tobacco
  - Addition of (b) mg/g (b)(4)
  - Addition of (b) mg/g (b)(4)
  - 47% decrease in (b)(4)
  - 47% decrease in (b)(4)
  - 34% increase in (b)(4)
  - 31% increase in (b)(4)
  - 23% decrease in (b)(4)
  - Addition of (b)(4)
  - Change in container closure system from zipper bag (polyethylene resin liner) to canister (polyethylene resin liner)

- **SE0017648**
  - 3 % increase in total tobacco
  - 150% increase in (b)(4)
  - Addition of (b) mg/g (b)
  - Addition of (b)(4)
  - 48% decrease in (b)(4)
  - 48% decrease in (b)(4)
  - 32% increase in (b)(4)
  - 29% increase in b)(4)
  - 2% increase in (b)(4) (humectant)

I concur with the conclusions of all the scientific reviews that the applicant has demonstrated that these differences in characteristics do not cause the new products to raise different questions of public health as described in Section 3 above. The new tobacco products have differences in tobacco blend (increases in (b)(4) and total tobacco), which can adversely affect smoke yields of harmful and potentially harmful constituents like benzo-a-pyrene, NNN and NNK. The increases in (b)(4) are offset by the larger decreases in (b)(4) which is anticipated to result in lower smoke yields of carbonyl byproducts during combustion. Similarly, the decrease in (b)(4), increase in potassium sorbate and addition of (b)(4) are changes that range from 0.032% to 3.2% of the tobacco filler weight. These differences are not anticipated to have measurable effect on smoke HPHC yields and therefore do not adversely affect the new tobacco products. The use of a different container closure system can affect the stability and

microbial activity of the new tobacco product, which may adversely affect the smoke yields of tobacco-specific nitrosamines. The applicant reports tobacco filler HPHC data for arsenic, ammonia, cadmium, benzo-a-pyrene, NNN, and NNK for the new and corresponding predicate tobacco products. These HPHCs are either analytically equivalent or decreased in the new tobacco products, demonstrating that the differences in the tobacco blend, preservatives, humectants, and container do not adversely affect the new tobacco products. Finally, the addition of (b)(4) (b)(4) (b)(4) in the new tobacco products is not a concern because the combustion temperatures are anticipated to be less than those needed to cause thermal degradation of these additives. Therefore, the differences in characteristics between the new and corresponding predicate products do not cause the new products to raise different questions of public health.

The predicate products meet statutory requirements because they were determined that they are grandfathered products (i.e., were commercially marketed in the United States as of February 15, 2007).

The new products are currently in compliance with the FD&C Act. I concur with these reviews and recommend that SE order letters be issued. FDA examined the environmental effects of finding these new products substantially equivalent and made a finding of no significant impact.

6. APPENDICES

APPENDIX A. NEW AND PREDICATE PRODUCTS

Common Attributes of SE Reports		
Submission date	August 20, 2020; August 21, 2020; and August 27, 2020	
Receipt date	August 20, 2020; August 21, 2020; and August 27, 2020	
Product manufacturer	Top Tobacco, LP	
Product category	Pipe Tobacco Products	
Product subcategory	Pipe Tobacco Filler	
Attributes[a]	**New Tobacco Product**	**Predicate Tobacco Product**
STN	**SE0017388**	**GF1804248**
Product name	4 ACES Turkish 6 oz. Medium Bag	Gambler Regular Medium Bag (6 oz)
Eligibility status	Not applicable	Grandfathered
Package type	Bag	Bag
Package quantity	6 oz	6 oz
Characterizing flavor	None	None
STN	**SE0017425**	**GF1804247**
Product name	Largo Bold 16 oz. Large Bag	Gambler Regular Large Bag (16 oz)
Eligibility status	Not applicable	Grandfathered
Package type	Bag	Bag
Package quantity	16 oz	16 oz
Characterizing flavor	None	None
STN	**SE0017626**	**GF1804247**
Product name	GAMBLER Turkish 16 oz. Large Bag	Gambler Regular Large Bag (16 oz)
Eligibility status	Not applicable	Grandfathered
Package type	Bag	Bag
Package quantity	16 oz	16 oz
Characterizing flavor	None	None
STN	**SE0017648**	**GF1804248**
Product name	LARGO Sun Grown 6 oz. Medium Bag	Gambler Regular Medium Bag (6 oz)
Eligibility status	Not applicable	Grandfathered
Package type	Bag	Bag
Package quantity	6 oz	6 oz
Characterizing flavor	None	None

Appendix B. Amendments

Submission Date	**Receipt Date**	**Applications being amended**	**Reviewed**	**Brief Description**
February 3, 2021	February 3, 2021	All STNs	Yes	Response to November 17, 2020, Deficiency Letter

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