

Technical Project Lead (TPL) Review:SE0003493 and SE0003494

SE0003493: Carnival Blue 100's Soft Pack	
Package Type	Soft Pack
Package Quantity	20 Cigarettes
Length	100 mm
Diameter	7.8 mm
Ventilation	20%
Characterizing Flavor	None
SE0003494: Carnival Silver 100's Soft Pack	
Package Type	Soft Pack
Package Quantity	20 Cigarettes
Length	100 mm
Diameter	7.8 mm
Ventilation	36%
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	KT&G Corporation
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Combusted Filtered
Recommendation	
Issue Substantially Equivalent (SE) orders.	

Technical Project Lead (TPL):

Digitally signed by Kenneth Taylor -S
Date: 2019.11.18 16:19:59 -05'00'

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

Signatory Decision:

- Concur with TPL recommendation and basis of recommendation
- Concur with TPL recommendation with additional comments (see separate memo)
- Do not concur with TPL recommendation (see separate memo)

Digitally signed by Matthew R. Holman -S
Date: 2019.11.19 06:50:35 -05'00'

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

TABLE OF CONTENTS

1. BACKGROUND	4
1.1. PREDICATE TOBACCO PRODUCTS	4
1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW.....	4
1.3. SCOPE OF REVIEW	6
2. REGULATORY REVIEW	6
3. COMPLIANCE REVIEW	7
4. SCIENTIFIC REVIEW	7
4.1. CHEMISTRY.....	7
4.2. TOXICOLOGY.....	8
4.3. BEHAVIORAL AND CLINICAL PHARMACOLOGY.....	9
5. ENVIRONMENTAL DECISION.....	9
6. CONCLUSION AND RECOMMENDATION	9

1. BACKGROUND

1.1. PREDICATE TOBACCO PRODUCTS

The applicant submitted the following predicate tobacco products:

SE0003493: Carnival Blue 100's Soft Pack	
Product Name	Carnival Lights 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 Cigarettes
Length	100 mm
Diameter	7.8 mm
Ventilation	29%
Characterizing Flavor	None
SE0003494: Carnival Silver 100's Soft Pack	
Product Name	Carnival Ultra Lights 100's Soft Pack
Package Type	Soft Pack
Package Quantity	20 Cigarettes
Length	100 mm
Diameter	7.8 mm
Ventilation	47%
Characterizing Flavor	None

The predicate tobacco products are combusted filtered cigarettes manufactured by the applicant.

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 21, 2011, FDA received two SE Reports from KT&G Corporation. FDA issued Acknowledgement letters to the applicant on September 6, 2011. FDA issued Advice/Information (A/I) Request letters on January 14, 2013. On April 10, 2013, FDA received an unsolicited amendment for all SE Reports to notify FDA of the applicant's late receipt of the A/I Request letters (SE0008210). FDA received responses to the A/I Request letters on May 2, 2013 (SE0008373 and SE0008374 respectively). On October 28, 2014, FDA held a teleconference with the applicant to request clarification of the First Commercial Marketing date. The applicant did not submit documentation providing the requested information. On June 11, 2015, FDA issued a Notification Letter indicating scientific review was expected to begin on July 26, 2015.

On October 19, 2015, FDA issued a Preliminary Finding (PFind) letter. On November 13, 2015, FDA received a request for a 20-day extension to respond to the PFind letter due to complexities of the matters involved in the response (SE0012598). On November 18, 2015, FDA received the applicant's response to the PFind letter for all SE Reports (SE0012647) and unsolicited amendments containing updates to all SE Reports (SE0012657 and SE0012658). On

November 19, 2015 FDA held a telecon with the applicant in which the applicant confirmed that it intends to withdraw its extension request. On December 21, 2015, FDA received an amendment with a request to withdraw the November 12, 2015 request for an extension to respond to the PFind letter (SE0012781). FDA issued an A/I letter on May 13, 2016.

On July 12, 2016, FDA received responses to the A/I letter (SE0013483). On May 12, 2017, FDA issued a PFind letter. On May 26, 2017, FDA received a 90-day PFind extension request for all SE Reports to conduct non-clinical and clinical studies to respond to the PFind letter (SE0014121). On June 9, 2017, FDA received partial responses to the PFind letter (SE0014142).

FDA issued an Extension Granted letter on June 15, 2017, with a response due date of September 9, 2017. On July 26, 2017, FDA received a meeting request to obtain clarification of the deficiencies stated in the May 12, 2017 PFind letter and obtain FDA concurrence as to the appropriateness of the applicant's proposed non-clinical and clinical studies (TC0002590).

On August 15, 2017, FDA received an unsolicited amendment from the applicant requesting a new response due date of April 30, 2021 to respond to the PFind letter to conduct clinical and non-clinical studies (SE0014239). On August 15, 2017, the applicant submitted an amendment withdrawing its request for an extension (SE0014245). On August 16, 2017, FDA issued a meeting granted letter and subsequently held the meeting on October 3, 2017. During the October 3, 2017 meeting, it was decided the applicant should submit an extension request with a revised timeline and plan in response to the May 12, 2017 PFind letter.

On November 16, 2017, FDA received an extension request from the applicant proposing to respond to the May 12, 2017 PFind letter by April 30, 2022 (SE0014403). On January 17, 2018, FDA issued a PFind Extension Granted letter¹ permitting a one-year extension with a response due date of January 17, 2019, to address Deficiency #4 in the May 12, 2017 PFind letter. On January 17, 2019, FDA received a response to the PFind letter (SE0015064). On April 1, 2019, FDA received the applicant's response to the Office of Compliance and Enforcement's (OCE) March 26, 2019 information request (SE0015154). On May 17, 2019, FDA issued a Deficiency letter.

On July 10, 2019, FDA received an extension request to respond by October 31, 2021 to the May 17, 2019, Deficiency letter (SE0015346). On October 8, 2019, FDA issued a Correction letter for the May 17, 2019, Deficiency letter which removed all deficiencies for SE0003493 and SE0003494².

¹ In this letter, FDA communicated the following to the applicant: "Given the proposed timelines in your extension request, FDA has chosen a staged approach to evaluate your responses to the deficiencies in the May 12, 2017 Preliminary Finding letter. The number of Harmful and Potentially Harmful Constituent (HPHC) level increases, listed in Deficiency 4, in the new products as compared with the corresponding predicate products, would need to be addressed to show that the new products do not raise different questions of public health. If you cannot address this particular deficiency, addressing the other deficiencies in the Preliminary Finding letter would not affect the overall determination of substantial equivalence. Thus, FDA will consider your rationale for why the HPHC increases do not cause the new products to raise different questions of public health first. If you are able to adequately and appropriately address Deficiency 4, FDA will consider your responses to the other deficiencies in the Preliminary Finding letter. If you successfully address Deficiency 4 and you need more time to address the other deficiencies, then you may be granted a second extension, at that time."

² In a July 8, 2019, memo titled "BCP Reviews of SE Reports Involving Changes in the Ventilation of Combusted Filtered Cigarettes", BCP determined that, based on review of the current literature and data, if a new product has an absolute increase

Product Name	SE Report	Amendments
Carnival Blue 100's Soft Pack	SE0003493	SE0008210 SE0008373 SE0010095 SE0012598 SE0012647 SE0012657 SE0012781 SE0013483 SE0014121 SE0014142 SE0014239 SE0014245 SE0014403 SE0015064 SE0015154 SE0015346
Carnival Silver 100's Soft Pack	SE0003494	SE0008210 SE0008374 SE0010095 SE0012598 SE0012647 SE0012658 SE0012781 SE0013483 SE0014121 SE0014142 SE0014239 SE0014245 SE0014403 SE0015064 SE0015154 SE0015346

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 Anne Martin on January 14, 2013, Paul Aguilar on

or an absolute decrease in ventilation of 12% or more from the predicate product, this change will likely result in a BCP deficiency.

April 18, 2014 and Rodney Hammond on November 12, 2019.

The final review 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 reviews³ dated December 23, 2015, 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.

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 Selvin H. Edwards on February 19, 2016, and on September 14, 2016⁴.

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:

³ Addendum reviews were completed on April 8, 2019, to clarify the package type and size for the predicate and new tobacco products. Since the initial grandfather determination on December 23, 2015, was based on a product of that package type and size, the addendum reviews do not change the conclusion of the initial determination.

⁴ A chemistry consult was completed on February 28, 2019, in which the previously evaluated HPHC data was re-evaluated using a Two One-Sided T-test (TOST); which is a statistical tool that calculates important analytical differences using the Horwitz-Thompson equation. The mean range of a TOST analysis is a measure of statistical probability that differences in a mean range of tested values are analytically significant. An equivalence margin at a 75% confidence interval reduces the number of inconclusive results, which default to be considered as not analytically equivalent.

- **SE0003493**
 - 99% increase in (b) (4)
 - Replacement of (b) (4)
 - 22% (ISO) and 19% (CI) increases in carbon monoxide

- **SE0003494**
 - 99% increase in (b) (4)
 - Replacement of (b) (4)
 - 15% (ISO) and 18% (CI) increases in carbon monoxide
 - 25% (ISO) increase in crotonaldehyde

The increase in (b) (4) can result in higher smoke yields of benzo- α -pyrene, and the use of (b) (4) can result in higher smoke yields of formaldehyde, acrolein, and benzene. The applicant provided ISO and Canadian Intense (CI) smoke regimen yields for these HPHCs, which are either less than or analytically equivalent in the new tobacco products compared to the corresponding predicate tobacco products. Therefore, the increased amounts (b) (4) and (b) (4) do not cause concerns. However, both new tobacco products have analytically significant increased smoke yields of carbon monoxide and crotonaldehyde, which is deferred to the Toxicology review for evaluation.

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. TOXICOLOGY

Toxicology reviews were completed by Steven B. Yee, on March 2, 2016, April 24, 2017, and on March 11, 2019⁵.

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:

- **SE0003493**
 - 22% (ISO) and 19% (CI) increases in carbon monoxide

- **SE0003494**
 - 15% (ISO) and 18% (CI) increases in carbon monoxide
 - 25% (ISO) increase in crotonaldehyde

The toxicology review considers the CI regimen to be more representative of the majority of smokers, and that for qualitative comparison purposes, decreases in HPHCs measured using the CI smoking regimen can offset HPHC increases obtained by the ISO smoking regimen. For this

⁵ The final Tox Review was amended on May 16, 2019 based on the applicant submitted a partial response (SE0015064) to the PFind letter addressing Deficiency #4 on January 16, 2019.

reason, the toxicology review considers the increases in carbon monoxide and crotonaldehyde ISO smoke yields to be offset by results obtained by the CI regimen⁶. Additionally, based on qualitative HPHC comparisons, the increase in risk of cardiovascular toxicity as a result of increased CI carbon monoxide smoke yields is mostly offset by the lowered cardiotoxicity risk associated with decreased and relatively highly toxic acrylonitrile. As a result, the increases in carbon monoxide and crotonaldehyde smoke yields do not cause toxicological concerns.

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.

4.3. BEHAVIORAL AND CLINICAL PHARMACOLOGY

Behavioral and clinical pharmacology reviews were completed by Kia J. Jackson on February 26, 2016, and on September 28, 2016⁷.

The final behavioral and clinical pharmacology 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 behavioral and clinical pharmacology perspective.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act for these provisional SE Reports (SE0003493 and SE0003494) is categorically excluded and, therefore, normally does not require the preparation of an environmental assessment (EA) or an environmental impact statement. FDA has considered whether there are extraordinary circumstances that would require the preparation of an EA and has determined that none exist.

6. CONCLUSION AND RECOMMENDATION

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

- **SE0003493**
 - 99% increase in (b) (4)
 - Replacement of (b) (4)
 - 22% (ISO) and 19% (CI) increases in carbon monoxide

- **SE0003494**
 - 99% increase in (b) (4)
 - Replacement of (b) (4)

⁶ For SE0003494, there is a 2% (or analytically equivalent) difference in crotonaldehyde CI smoke yields between the new and corresponding predicate tobacco products.

⁷ The final BCP was amended on August 15, 2019 based on the memorandum "BCP Reviews of SE Reports Involving Changes in the Ventilation of Combusted Filtered Cigarettes," July 8, 2019.

- 15% (ISO) and 18% (CI) increases in carbon monoxide
- 25% (ISO) increase in crotonaldehyde

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco products to raise different questions of public health. The increase in (b)(4) can result in higher smoke yields of benzo- α -pyrene, and the use of (b)(4) can result in higher smoke yields of formaldehyde, acrolein, and benzene. However, the ISO and Canadian Intense (CI) smoke regimen yields for these HPHCs are either less than or analytically equivalent in the new tobacco products compared to the corresponding predicate tobacco products. Therefore, the increased amounts (b)(4) and (b)(4) do not cause concerns. The toxicology review considers the CI regimen results to be more representative of actual consumer smoking, and therefore, considers these smoking regimen HPHC results to offset those obtained by the ISO regimen. As a result, the increases in the ISO smoke yields of carbon monoxide and crotonaldehyde are not considered to be a concern. The toxicological effects of the increases in the CI smoke yields of carbon monoxide are offset by the decreases in the more toxic acrylonitrile amounts for both new 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 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).

Because the proposed action is issuing SE orders for the provisional SE Reports, it is a class of action that is categorically excluded under 21 CFR 25.35(a). FDA has considered whether there are extraordinary circumstances that would require the preparation of an environmental assessment and has determined that none exist. Therefore, the proposed action does not require preparation of an environmental assessment or an environmental impact statement.

SE order letters should be issued for the new tobacco products in SE0003493 and SE0003494, as identified on the cover page of this review.