Technical Project Lead (TPL) Review: SE0002700-SE0002706, SE0002708, and SE0002709

SE0002700: Crowns Blue 100s Box[1]	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter[2]	7.75 mm
Ventilation	47%
Characterizing Flavor	None
SE0002701: Crowns Blue King Box	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.75 mm
Ventilation	47%
Characterizing Flavor	None
SE0002702: Crowns Gold 100s Box[1]	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	18%
Characterizing Flavor	None
SE0002703: Crowns Gold King Box	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.75 mm
Ventilation	18%
Characterizing Flavor	None
SE0002704: Crowns Menthol Dark Green 100s Box[1]	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	6%
Characterizing Flavor	Menthol

[1] There is an interchangeable use of the words "100s" and "100's" in the new tobacco product name.
[2] The applicant submitted the circumference which allowed for a calculation of diameter.

SE0002705: Crowns Menthol Green 100s Box[1]	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	18%
Characterizing Flavor	Menthol
SE0002706: Crowns Menthol Green King Box	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.75 mm
Ventilation	18%
Characterizing Flavor	Menthol
SE0002708: Crowns Red 100s Box[1]	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	6%
Characterizing Flavor	None
SE0002709: Crowns Red King Box[3]	
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.75 mm
Ventilation	14%
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	Commonwealth Brands, Inc.
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Combusted Filtered
Recommendation	
Issue Not Substantially Equivalent (NSE) orders.	

[3] There is an interchangeable use of the words "King" and "Kings" in the new tobacco product name.

Technical Project Lead (TPL):

Digitally signed by Matthew J. Walters -S
Date: 2019.06.07 09:17:23 -04'00'

Matthew J. Walters, Ph.D., MPH
Commander, 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)

Digitally signed by Matthew R. Holman -S
Date: 2019.06.07 09:32:57 -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:

SE0002700: Crowns Blue 100s Box	
Product Name	USA Gold Ultra Lights 100's Box[4]
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	47%
Characterizing Flavor	None
SE0002701: Crowns Blue King Box	
Product Name	USA Gold Ultra Lights Kings Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.85 mm
Ventilation	47%
Characterizing Flavor	None
SE0002702: Crowns Gold 100s Box	
Product Name	USA Gold Lights 100's Box[4]
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	22%
Characterizing Flavor	None
SE0002703: Crowns Gold King Box	
Product Name	USA Gold Lights Kings Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.85 mm
Ventilation	14%
Characterizing Flavor	None

[4] There is an interchangeable use of the words "100s" and "100's" in the predicate tobacco product name.

SE0002704: Crowns Menthol Dark Green 100s Box	
Product Name	USA Gold Full Flavor Menthol 100's Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	6%
Characterizing Flavor	Menthol
SE0002705: Crowns Menthol Green 100s Box	
Product Name	USA Gold Menthol Lights 100's Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	22%
Characterizing Flavor	Menthol
SE0002706: Crowns Menthol Green King Box	
Product Name	USA Gold Menthol Lights Kings Soft Pack
Package Type	Soft Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.85 mm
Ventilation	14%
Characterizing Flavor	Menthol
SE0002708: Crowns Red 100s Box	
Product Name	USA Gold Full Flavor 100's Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	99 mm
Diameter	7.75 mm
Ventilation	6%
Characterizing Flavor	None
SE0002709: Crowns Red King Box	
Product Name	USA Gold Full Flavor Kings Box
Package Type	Hard Pack
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.85 mm
Ventilation	6%
Characterizing Flavor	None

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

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

On March 21, 2011, FDA received nine SE Reports from Commonwealth Brands, Inc. The applicant re-submitted the SE Reports (TC0000093) on April 5, 2011, received April 6, 2011, because the original submissions were password protected. FDA issued Acknowledgement letters on August 26, 2011, for SE0002704 - SE0002706 and on September 15, 2011, for SE0002700 - SE0002703, SE0002708 and SE0002709. FDA issued Advice/Information Request (A/I) letters for SE0002700-SE0002702 and SE0002704 on January 14, 2013 and for SE0002703,[5] SE0002705, SE0002706, SE0002708 and SE0002709 on January 22, 2013. FDA received the applicant's response to the A/I letters on February 13, 2013 (SE0007293-SE0007296) for SE0002700-SE0002702 and SE0002704, and on February 28, 2013 (SE0007511, SE0007512, SE0007514 and SE0007515) for SE0002705, SE0002706, SE0002708 and SE0002709. On October 16, 2014, FDA received unsolicited amendments (SE0010712 and SE0010713) containing correction to ventilation information for SE0002708 and SE0002704, respectively. FDA issued a Notification letter on January 11, 2016, indicating scientific review was expected to begin on February 25, 2016. On February 24, 2016, FDA received an amendment (SE0012956) containing additional information and replacing some of the previous information provided on March 22, 2011, for all of the SE Reports. FDA issued an A/I letter for all of the SE Reports on June 2, 2016. On July 28, 2016, FDA received the applicant's response to the A/I letter (SE0013545). On August 4, 2016, FDA had a telecon with the applicant to request a translation for the foreign language section in their July 28, 2016, response to the A/I letter, as FDA does not evaluate any documents in a foreign language unless a certified translation is included. On August 11, 2016, FDA received an amendment (SE0013569) containing English translation for test report submitted in the applicant's July 28, 2016, response to the A/I letter. FDA issued a Preliminary Finding (PFind) letter for all of the SE Reports on October 17, 2016. On November 15, 2016, FDA received the applicant's response to the PFind letter (SE0013746) for all of the SE Reports. On March 31, 2017, FDA received a late amendment (SE0014013) containing additional information in response to the PFind letter dated October 17, 2016. Although FDA received this amendment after the response due date, FDA reviewed the late amendment in conjunction with the Technical Project Lead's (TPL) review of all information submitted by the applicant because the review of this amendment (received in 2017) does not further delay FDA's continued review of these SE Reports. FDA determined that the review of the late amendment does not alter the conclusion of the TPL review. FDA developed addendums to the final scientific reviews to incorporate information contained within this late amendment.

Product Name	SE Report	Amendments
Crowns Blue 100s Box	SE0002700	TC0000093 SE0007293 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013

[5] For SE0002703, the applicant did not submit a response to the January 22, 2013, A/I letter by the response due date. Upon further investigation, FDA identified that the applicant did not receive the January 22, 2013 A/I letter. Due to an oversight, FDA never reissued the A/I letter. Nonetheless, the applicant provided information requested in the January 22, 2013, A/I letter in the later amendments during scientific review of this SE Report.

Product Name	SE Report	Amendments
Crowns Blue King Box	SE0002701	TC0000093 SE0007294 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013
Crowns Gold 100s Box	SE0002702	TC0000093 SE0007295 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013
Crowns Gold King Box	SE0002703	TC0000093 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013
Crowns Menthol Dark Green 100s Box	SE0002704	TC0000093 SE0007296 SE0010713 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013
Crowns Menthol Green 100s Box	SE0002705	TC0000093 SE0007511 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013
Crowns Menthol Green King Box	SE0002706	TC0000093 SE0007512 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013
Crowns Red 100s Box	SE0002708	TC0000093 SE0007514 SE0010712 SE0012956

Product Name	SE Report	Amendments
		SE0013545 SE0013569 SE0013746 SE0014013
Crowns Red King Box	SE0002709	TC0000093 SE0007515 SE0012956 SE0013545 SE0013569 SE0013746 SE0014013

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 Stephanie Durkin on January 14, 2013 and January 22, 2013; by Laila Noory on April 22, 2014 and April 27, 2014; and by Grace Kaiyuan on March 23, 2018.

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 March 4, 2016, 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 Youbang Liu on May 11, 2016, and An Vu, on October 4, 2016, and January 5, 2017.

An addendum review dated July 5, 2018, contains additional chemistry review of the amendment (SE0014013) and concludes that the new tobacco products have different characteristics related to product composition 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 addendum review identifies the following deficiencies that have *not* been adequately resolved:

1. All of your SE Reports contain discrepancies in the quantity of each tobacco blend component of the new and corresponding predicate products in your November 2016 (SE0013746) and March 2017 (SE0014013) amendments. The quantities of the tobacco blend components of the new products and the surrogate new products reported in appendices to your response to Deficiencies 2, 5, 9 and 11 of the Preliminary Finding Letter contained in amendment SE0013746, and reiterated in amendment SE0014013, are inconsistent with the tobacco blend components of the new products reported in your response to Deficiency 7. Specifically, the tobacco blend quantities for the new and surrogate new products provided in amendment SE0014013 are identical to quantities provided in the response to Deficiencies 2, 5, 9 and 11 but different from the quantities provided in response to Deficiency 7. In addition, the quantities of the tobacco blend components of the predicate and surrogate predicate products provided in amendment SE0014013 are inconsistent with the quantities provided for the predicate products in your response to Deficiency 7. Furthermore, the total tobacco blend weights, which are the sum of the quantities of the individual tobacco components provided in your response to Deficiency 7, are higher in the new and predicate products compared to the average tobacco filler mass, which consist of tobacco and non-tobacco ingredients included in your response to Deficiency 2. However, the total weights of the tobacco blend (tobacco only) for the new, surrogate new, predicate and surrogate predicate products provided in amendment SE0014013 are lower by 11-25% compared to the total tobacco weight determined from your response to Deficiency 7. Your SE Reports do not provide any indication that the amounts of (b) (4) increased to compensate for the lower mass or that cigarette dimensions changed to accommodate the smaller volume of material. Therefore, your response does not provide a rationale to explain the inconsistencies in tobacco blend composition. This information would be helpful for FDA to determine whether the menthol and HPHC data provided can be extrapolated from the surrogate new and predicate products to the new and predicate products, respectively. Explain these discrepancies and provide the correct quantity of each tobacco blend component of the new, surrogate new, predicate and surrogate predicate products.

2. SE0002700 – SE0002706 and SE0002708 has higher tobacco cut filler cadmium and arsenic in one or more surrogate new products compared to the corresponding surrogate predicate products. However, your SE Reports do not include smoke measured arsenic and cadmium smoke yields. Higher toxic metals levels in the tobacco cut filler can lead to higher smoke toxic metal levels and can cause the new products to raise different questions of public health. This information would be help FDA determine whether the data from the surrogate new and surrogate predicate products can be extrapolated to the new and predicate products and whether the new products raise different questions of public health.[6] Provide a rationale for why higher cut filler arsenic and cadmium in SE0002700 – SE0002706 and

(b)(5) Deliberative Process

SE0002708 does not cause the new products to raise different questions of public health. One way to address this issue is to provide the mainstream smoke yields of arsenic and cadmium for the surrogate products of SE0002700 – SE0002706 and SE0002708 by the ISO and Canadian Intense machine-smoking regimen. If you select this option, provide the following information about HPHC testing so that we can fully evaluate the HPHC data:

a. Reference product datasets (e.g., 1R6F)
b. Quantitative test protocols and method used.
c. Testing laboratory and their accreditation(s).
d. Length of time between date(s) of manufacture and date(s) of testing.
e. Number of replicates.
f. Standard deviation(s).
g. Complete data sets.
h. A summary of the results for all testing performed.
i. Storage conditions prior to initiating testing.

If your test methods are national or international test standards, identify any deviations from those standards.

The chemistry reviewer identified an issue (deficiency 1) in which there were inconsistencies in the tobacco blends between information provided by the applicant in its response to the PFind letter (SE0013746) and its March 31, 2017 amendment (SE0014013). OS' practice at this time is to review information in the latest amendment, and this information will supersede any information that was provided previously. Therefore, the information related to the tobacco blends in the amendment (SE0014013) supersedes previous tobacco blend information, including the information provided in the response to Deficiency 7 of the PFind Letter. In this case, I have reviewed the tobacco blend information provided in the amendment (SE0014013) which allowed a comparison of the tobacco blends, ingredients, and other features enabling bridging between the surrogate products and the new and predicate tobacco products. I concluded that the surrogate tobacco products are acceptable. Therefore, deficiency 1 should not be conveyed to the applicant. Tobacco blend can have an appreciable impact on HPHC yields; however, the chemistry reviewer did not identify any concerns in the HPHC methodology used. The differences in the HPHCs were deferred to toxicology for the final evaluation of the HPHC yields. The chemistry reviewer did identify an issue with the applicant failing to measure cadmium and arsenic in the smoke of these tobacco products (deficiency 2) which should still remain as indicated above.

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.

4.2. ENGINEERING

Engineering reviews were completed by Tiffany Petty on May 6, 2016, Beth Tirio on October 11, 2016, and Julie Morabito on January 3, 2017.

An addendum review, dated July 5, 2018, contains additional engineering review of the amendment (SE0014013) and 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 addendum review identifies the following deficiencies that have *not* been adequately resolved:

1. All of your SE Reports provide information on the design parameters for the predicate and new products. However, your SE Reports do not include all of the design parameters necessary to fully characterize the predicate and new products. In order to adequately characterize the products, it is necessary to compare key design parameters. Provide the **upper and lower range limits** for denier per filament for each new and predicate product.

   You provide target specifications and range limits for overall cigarette draw resistance that were calculated from test datasets generated from testing of the new and predicate products. In addition, you state that the filter density target specifications were calculated from measured values and the overall cigarette draw resistance target specifications are average measured values. However, a target specification is the exact manufacturing standard to which a parameter must conform, rather than the outcome of the manufacturing process. The information you provided represents the actual outcome of the manufacturing process and, therefore, is not valid for use as target specifications. Provide the **target specification and upper and lower range limits** for *all* of the following cigarette design parameter for each new and predicate product:

   a. Overall cigarette draw resistance (mm H_2O) and
   b. Filter density (g/cm^3).

   For each of the above parameters, provide the necessary data on a per unit of product basis (e.g., cigarette draw resistance should be reported in mm H_2O per cigarette).

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

   Note that filter density, denier per filament, and total denier are necessary because filter efficiency (%) was not provided. As an alternative to submitting the information described above for filter density, denier per filament, and total denier, you may provide target specification and upper and lower range limits for filter efficiency.

2. All of your SE Reports include design parameter specifications but do not include data confirming that specifications are met. You indicate through labeling of your tables and data that the new products were used to generate the data provided in response to the October 2016 Preliminary Finding letter. However, since you state that you use surrogate products for the new products, it is unclear whether the test data provided is from the new product or from the surrogate products. Clarify whether the data provided for puff count, draw resistance, filler mass, and filter ventilation are based on new products or surrogate new products.

   You provide tobacco filler oven volatile test data as an average of averages, which does not allow for a comparison of the design parameter test data with the target specification and

range limits. In addition, you do not provide summary data, maximum, minimum, standard deviation, or test protocols for filter density for the new and predicate product for all of the SE Reports. In addition, you use a surrogate product in place of the new product for puff count, overall cigarette draw resistance, tobacco filler mass, and filter ventilation, and you provide information to suggest that the new products and the corresponding surrogate new products have nearly identical design parameters. However, as explained in another deficiency, you do not provide complete characteristics needed to determine whether HPHC data can be extrapolated from the surrogate new products to the new products.

All of your SE Reports also provide some, but not all, of the necessary test data for the tobacco filler mass and filter density of each new and predicate product. You state that test data for each of these two design parameters is calculated based on other design parameters and you provide descriptions of the calculations used to determine the test data values for tobacco filler mass and filter density. Calculated test data for tobacco filler mass are based on subtracting the target specifications of the mass of each of the non-tobacco components from the average overall cigarette mass. Tobacco filler mass test data that is calculated from target specifications, as opposed to actual measured values, does not accurately identify the tobacco filler mass of a sample of individual cigarettes. The calculated test data for filter density are based on measured values of other design parameters. However, you provide only a single data point for filter density for each new and predicate product, and you do not provide maximum and minimum values or a standard deviation value, acceptance criteria, or test protocols for each measured value that contributes to the calculation of filter density. Therefore, for all of your SE Reports, the test data provided for tobacco filler mass and filter density cannot be used to confirm whether the design parameter specification has been met.

For all SE Reports, additional test data is needed for the new and predicate products in order to confirm whether design parameter specifications have been met. Provide the test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for all of the following cigarette design parameters for each predicate and new product, unless noted:

a. Overall cigarette draw resistance (mm H_2O)
b. Tobacco filler mass (mg)
c. Tobacco filler oven volatiles (%)
d. Filter density (g/cm^3)

For each of the above parameters, provide the necessary data on a per unit of product basis (e.g., tobacco filler mass should be reported in mg per cigarette).

For parameters for which you have reported average of averages, you may satisfy a portion of this deficiency by providing the measured values and summary data that was used to determine the average of averages data. For parameters for which you have reported calculated data, each of the calculated values must be based on the actual measured values of design parameters, rather than target values of design parameters.

COAs from the material supplier may satisfy this deficiency. If you choose to address this deficiency by providing COAs for any of the parameters listed above, the COAs must include

target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

Additionally, for the design parameters listed above that were tested according to national or international standards, identify the standards and state what deviations, if any, from the standards occurred.

3. All of your SE Reports include COAs to confirm that cigarette paper base paper basis weight, cigarette paper base paper porosity, and, where applicable, cigarette paper band porosity target specifications have been met. In addition, all of your SE Reports include COAs to confirm that total denier and denier per filament target specifications have been met. However, some of the COAs cannot be used because they do not contain all of the necessary information, described below:

    - Cigarette paper base paper basis weight and base paper porosity COAs
        - SE0002700, SE0002702, SE0002706, SE0002709: COAs for the new and predicate products do not include acceptance criteria.
        - SE0002701, SE0002703-SE0002705, SE0002708*:* COAs for the new product do not include acceptance criteria. COAs for the predicate product are not provided. Email correspondence between you and your material supplier is provided.

    - Cigarette paper band porosity COAs
        - All SE Reports: COAs for the new product do not include acceptance criteria.

    - Filter total denier COAs
        - SE0002700, SE0002701, SE0002704, SE0002708*:* COAs for the new and predicate products do not include maximum and minimum or standard deviation values of the test data.
        - SE0002702, SE0002703, SE0002705, SE0002706, SE0002709: COAs for the new product do not include maximum and minimum or standard deviation values of the test data.

    - Filter denier per filament COAs
        - SE0002700, SE0002701: COAs for the new and predicate products do not contain acceptance criteria, maximum and minimum, or standard deviation of the test data.
        - SE0002702, SE0002703, SE0002705, SE0002706, SE0002709: COAs for the new product do not contain acceptance criteria, maximum and minimum, or standard deviation of the test data.
        - SE0002704, SE0002708: COAs for the new and predicate products do not include maximum and minimum or standard deviation values of the test data.

    For all SE Reports, additional test data is needed for the new and predicate products in order to confirm whether design parameter specifications have been met. If you choose to address this deficiency by providing COAs for any of the parameters listed above, the COAs

must include target specification; quantitative acceptance criteria; parameter units; test data average value; and either the standard deviation of the test data or the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

4. All of your SE Reports include test data for filter ventilation for the new and corresponding predicate products, but the data do not confirm that the target specification for filter ventilation has been met. You state that the filter ventilation test data is for informational purposes and not intended to assess whether design parameter specifications for filter ventilation have been met. However, test data are necessary to confirm whether design parameter specifications have been met, and differences in filter ventilation influence smoke constituent yields. In addition, the data provided in response to the October 2016 Preliminary Finding letter contains filter ventilation test data for each new and predicate product. For SE0002700-SE0002703, SE0002705-SE0002706, and SE0002709, the new and predicate product datasets have multiple data points which fall outside of the specified range limits. Similarly, for SE0002704 and SE0002708, the predicate product datasets have multiple data points which fall outside of the specified range limits. Provide a method that explains your handling of products that do not conform to the design parameter specifications.

   Furthermore, for SE0002704 and SE0002708, the target specifications and range limits for filter ventilation are identical between the new and predicate product. However, the test data for the new product indicates that the filter ventilation of the new product is actually lower than the filter ventilation of the corresponding predicate products for these two SE Reports. This discrepancy suggests that the target specifications and range limits provided for the new and predicate products in SE0002704 and SE0002708 do not accurately characterize the new and predicate products of these SE Reports. Without summary test data, it is not clear whether the filter ventilation for the new product indicates that the actual filter ventilation of the new products is lower than the actual filter ventilation of the predicate products. A decrease in filter ventilation typically leads to increases in smoke constituent yields. Therefore, clarify and provide an explanation for the discrepancy between the target specification and range limits for the new and predicate products. Also, provide a method by which you address filter ventilation test data that fall outside of the specified range limits for filter ventilation.

5. All of your SE Reports include clarification that the filter pressure drop value reported corresponds to the expected filter rod (b) (4)) pressure drop divided by four to correspond to filter tip pressure drop. However, you have not clarified whether the expected value is a measured value or if the value is theoretical and calculated using other design parameters. Calculated or theoretical values are not appropriate for use as test data. If the value for filter pressure drop is an average value from measured test data, provide the test protocol, quantitative acceptance criteria, data set, and full summary of the results for each SE Report. If the value is a theoretical value, provide complete test data with measured values, as theoretical values are not acceptable for use as test data to confirm whether design parameter specifications have been met.

6. All of your SE Reports indicate design differences between the new and corresponding predicate products that may cause an increase in smoke constituent yields. You provided

tar, nicotine and carbon monoxide (TNCO) yields for each SE Report; however, the TNCO yields you provide were collected using a surrogate tobacco product in place of the new product and it is not clear whether the surrogate new product test data can be extrapolated to the new product for each SE Report. As such, the TNCO yields you provide may not be used as a justification for the following differences in design parameters for the SE Reports listed:

a. Decrease in tobacco oven volatiles (moisture) in all SE Reports by 11%
b. Decrease in tobacco rod density in SE0002701, SE0002704, SE0002708 and SE0002709 by between 9% and 10%
c. Increase in cigarette paper base paper basis weight in SE0002701, SE0002703-SE0002705, and SE0002708 by 16%
d. Decrease in cigarette paper band porosity in SE0002700, SE0002702, and SE0002709 by 15%
e. Decrease in filter total denier in SE0002701-SE0002703, SE0002705, SE0002706, and SE0002709 by between 14% and 17%
f. Decrease in denier per filament in all SE Reports by between 11% and 22%
g. Decrease in filter pressure drop in SE0002701-SE0002706, and SE0002708 by between 9% and 15%
h. Decrease in filter ventilation in SE0002702 and SE0002705 by 29%[7]

All of these design parameter differences may increase smoke constituent yields and influence other design parameters. Provide scientific evidence and a rationale for why the differences in design parameters do 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 an engineering perspective.

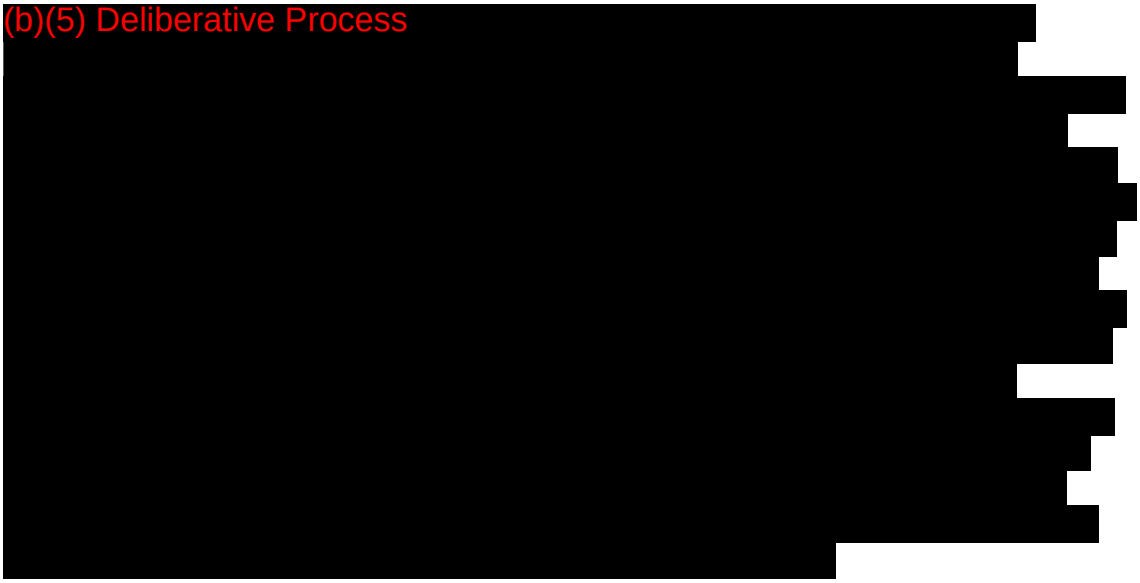
(b)(5) Deliberative Process [redacted]

Deficiencies 1 through 6 (b)(5) Deliberative Process [redacted]

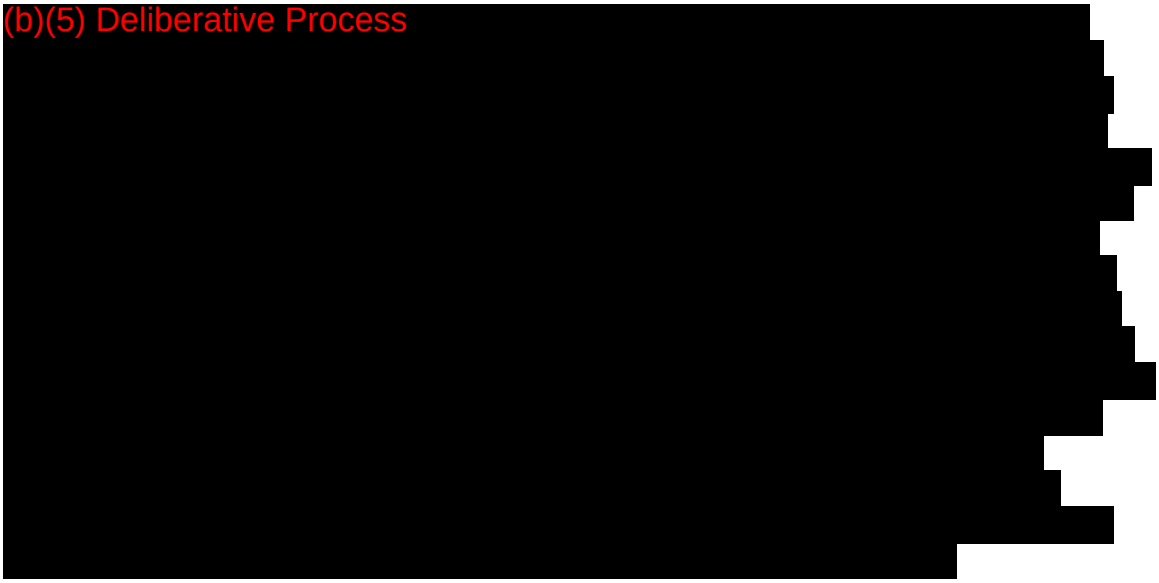
[7] The addendum review erred in stating that there was a 29% decrease in filter ventilation in the new tobacco product in SE0002705. The correct percentage is 18%

[8] See the March 1, 2019 Memorandum, Engineering Review of Substantial Equivalence (SE) Reports for Originally Regulated Products

(b)(5) Deliberative Process



(b)(5) Deliberative Process



(b)(5) Deliberative Process

(b)(5) Deliberative Process

(b)(5) Deliberative Process

(b)(5) Deliberative Process

(b)(5) Deliberative Process

4.3. TOXICOLOGY

Toxicology reviews were completed by Prince Awuah on May 13, 2016, October 13, 2016, and March 24, 2017.[9,10]

The addendum review dated August 1, 2018, concludes that the new tobacco products have different characteristics related to product toxicity 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.

[9] An addendum review was completed on May 4, 2017, to update deficiency 1 in the March 24, 2017, review. Information supplied by the applicant concerning all SE Reports indicated that new ingredients had been added to the new tobacco products compared to the corresponding predicate tobacco products. These added ingredients were listed in alphabetical order in the review but a formatting error occurred with the list. The addendum adjusts the formatting of the list and should be included in the NSE orders.

[10] An addendum review was completed on August 1, 2018, in order to review the late amendment (SE0014013) received by FDA on March 31, 2017. Another addendum review was completed on April 4, 2019, to update HPHC analysis.

The addendum review identifies the following deficiencies that have *not* been adequately resolved:

1. SE0002700, SE0002704, SE0002706, and SE0002709 provide lists of the tobacco and ingredients added to the "Master Subject" and surrogate predicate products which represent the new and predicate products. You also provided HPHC values under the ISO and HCI smoking regimens for the Master Subject and corresponding surrogate predicate products. Based on the HPHC values you provided, CTP identified the following increases in filler and smoke yields from the Master Subject products when compared to the corresponding surrogate predicate products under the specified smoking regimens:[11]

   - SE0002700: Formaldehyde (CI: 31%); cadmium (36%)
   - SE0002704: Cadmium (25%)
   - SE0002706: Cadmium (24%)
   - SE0002709: NNK (CI: 35%); cadmium (28%)

   These HPHC increases can result from tobacco blend changes as well as ingredients added to tobacco and structural materials in the new products. The following ingredients that are added to or increased in the new products may contribute to the generation of HPHCs noted above when combusted:

   a.
   b.
   c.
   d.
   e.
   f.
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   i.
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   k.
   l.
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   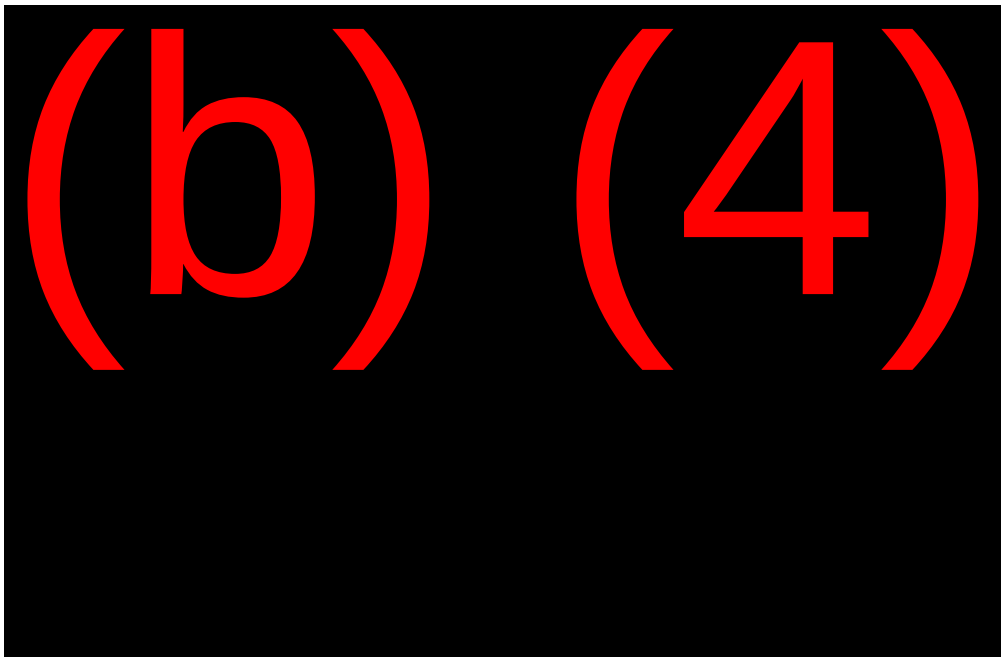

   Exposures to the HPHCs listed above have been associated with cancer and noncancer adverse health effects. You voluntarily submitted quantitative risk assessments (QRAs) and

[11] The percentage increases in Cadmium for SE0002700, SE0002704, SE0002706 and SE0002709 are increases noted in the tobacco filler and not in smoke yields.

probabilistic risk assessments (PRAs) to support your position that increases in HPHC levels as a result of tobacco blend and tobacco ingredient changes do not cause the new product to raise different questions of public health.

While a QRA/PRA is not required for an SE Report, such analyses can inform the review process if adequately described, supported with details and justifications. For FDA to review any risk assessment that is voluntarily provided in an application, submit a detailed account of the QRA, in line with recommendations from the National Academy of Sciences must be provided. In addition, provide all data, methods and a detailed description of the results and analysis of the QRA and PRA to demonstrate that user exposure to the Master subject products will not lead to increased toxicity or overall health risk compared to the corresponding surrogate predicate products. The data, results, and analysis of the QRAs and PRAs you provided are limited because they are either unclear or lack sufficient details.

a. Provide specific evidence or rationale for the inclusion of body weight and daily inhalation rate in your exposure estimation regarding the smoker exposure scenario. In addition, provide clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime is appropriate for the specific products and expected user populations.

b. Provide detailed selection criteria for the selection of all reference values and scientific evidence for deviating from established reference values. Include additional evidence or rationale for the selected reference values, given the availability of multiple reference values for a specific constituent. In addition, provide evidence that the reference values used in the calculation of the HQ or ILCR, in both the QRAs and PRAs, are appropriate for the toxicological endpoints associated with the use of the new and predicate products and for the expected product user populations.

c. Provide a detailed description of how the calculated HQ or ICLR ratios between the respective new and predicate product[12] HPHCs can be used to determine whether the new products raise different questions of public health.

d. In the 'Problem Formulation' section, you state that "*the risk assessment (i.e., QRA) presented herein does not concern absolute risk or hazard but rather the comparative risk or hazard between the two products.*" However, you provided data and a discussion relating to the absolute risk or hazard (e.g., the total cancer risk or margin-of-exposure). Provide clear description of how you intend to characterize and interpret the QRA and PRA results.

e. Provide a complete description of the PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. Provide scientific evidence and rationale demonstrating that the distributions for

[12] Or surrogate new/surrogate predicate products

each parameter and the ranges are appropriate, given the characteristics of the new and predicate products and the anticipated user population of both products. Consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions. Any rationale or scientific evidence needs to also include further discussion as to the quality and appropriateness of the inputs as well as the PRA expectations that the resulting parameter estimations accurately reflect the real product or user specific values.

Additionally, the submitted PRA, which relies on the same parameters in the QRA, the distributions and distribution parameters used in the exposure analyses were not adequately described. The current PRAs do not provide 1) the degree of certainty of risk estimates, 2) sufficient characterization of the uncertainty surrounding all critical elements of risk assessments, 3) insight regarding how the risk estimates vary among different percentiles of an exposed population, including sensitive populations or life stages, and 4) description of the key contributors to variability or uncertainty in predicted exposures or risk estimates. You conduct simulations using distributions for population and behavioral parameters, such as cigarettes per day (CpD) and inhalation rates. This type of analysis is useful in examining what factors may impact an individual smoker's risk the most, as noted in your sensitivity analyses. You need to provide scientific evidence and rationale demonstrating that the distributions for each parameter and the ranges are appropriate given the characteristics of the new and predicate products and the anticipated user population of both products. Any rationale or scientific evidence needs to include discussion as to the quality and appropriateness of the inputs as well as the PRA expectations that the resulting estimations accurately reflect the new and predicate specific values. For example, the distribution of cigarettes per day is listed as 1-95, but you do not provide specific data or rationale showing this is a representative range for the Master Subject product or surrogate predicate products. This example is particularly important as it is, according to sensitivity analyses, the biggest driver of variability. Additionally, you did not specify if results of the cumulative ILCR and HI are based on mean estimated values or across a distribution, which would allow for comparisons across a range of percentiles. Comparisons of upper percentiles (e.g. 90th or 95th percentiles), for example, may likely better capture the potential differences in health risks for users that may occur. In SE0002700, the smoke yield of carcinogenic formaldehyde was increased in the Master Subject product beyond the analytically equivalent levels under the HCI smoking condition; and carcinogenic NNK was increased beyond analytically equivalent levels in the Master Subject products described in SE0002700, SE0002703 SE0002708 [13]and SE0002709 which contributes to an increase in cancer risk from cigarette which exceeds the estimated risk for surrogate predicate products. Provide new scientific evidence and a rationale that the HPHC increases

[13] SE0002704 and SE0002706 should have been identified as the SE Reports of concern and not SE0002703 and SE0002708. This has been corrected in the letter ready comments.

associated with tobacco blend and ingredient changes in the SE Reports listed above do not cause the new products to raise different questions of public health.

2. SE0002703 and SE0002708, you provide lists of the tobacco and ingredients added to the "Master Subject" and surrogate predicate products which represent the new and predicate products. You also provided HPHC values under the ISO and HCI smoking. Based on the HPHC values you provided, CTP identified the following increases in filler and smoke yields from the Master Subject products when compared to the corresponding surrogate predicate products under the specified smoking regimens:

   - SE0002703: NNK (ISO: 37%; CI: 31%); cadmium (26%)[14]
   - SE0002708: NNK (ISO: 28%)

   These HPHC increases can result from tobacco blend changes as well as ingredients added to tobacco and structural materials in the new products. The following ingredients that are added to or increased in the new products may contribute to the generation of HPHCs noted above when combusted:

   a.
   b.
   c.
   d.
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   f.
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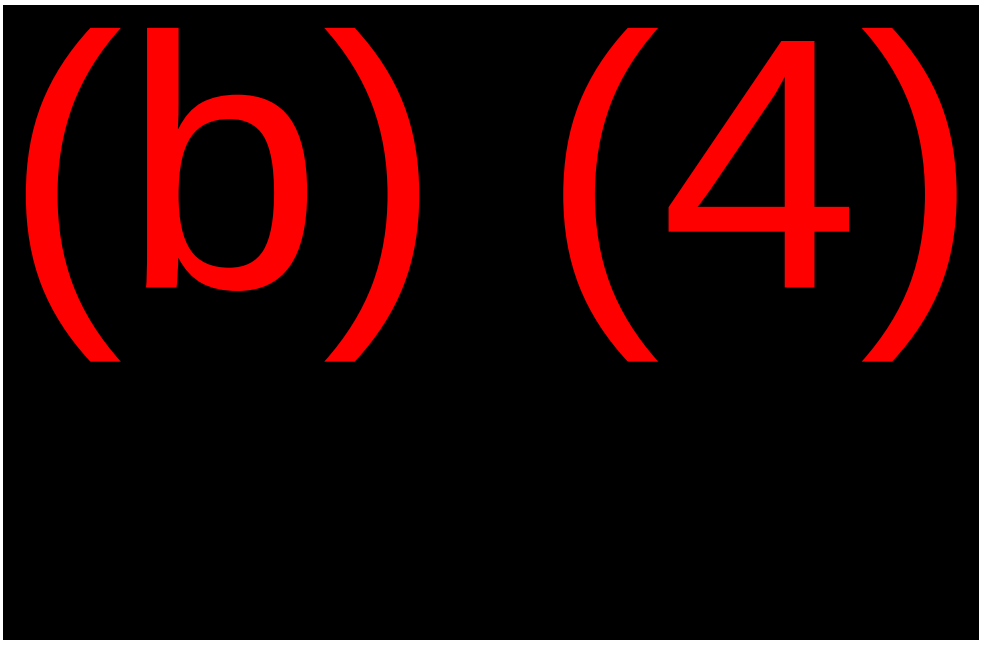

   A risk assessment approach is unlikely to demonstrate that the new products in these SE Reports do not raise different questions of public health because there are only HPHC increases and no concomitant HPHC decreases compared to the surrogate predicate product and therefore there are no decreased risks that could offset the cancer risk and noncancer hazard associated with the HPHC increases associated with the new product. Provide new scientific evidence and a rationale that the HPHC increases associated with

[14] This is a percentage increase noted in the tobacco filler and not in smoke yield.

tobacco blend and ingredient changes in the SE Reports listed above do 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 toxicology perspective.

4.4. SOCIAL SCIENCE

A social science review was completed by Jennifer Bernat on May 9, 2016.

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 difference:

- Change from a soft pack to a hard pack (SE0002701 and SE0002706 only)

The social science review noted that there is a lack of peer reviewed research specifically examining consumer perceptions of harm and appeal of cigarettes packaged in a soft pack versus a hard pack. The limited industry data were inconclusive. One study suggested that the new tobacco product may not raise different questions of public health beyond the predicate tobacco product (soft packs were perceived as milder and less harsh). Another study reported increased appeal; however, consumers seemed to like both soft and hard packs. The social science review concludes that this change does not cause the new tobacco products to raise different questions of public health. I agree with the social science review because this modification does not change the consumable portion of the cigarette, nor is it expected to impact moisture or leach any materials into the new tobacco product. 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 social science perspective.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order finding a tobacco product not substantially equivalent (NSE) under section 910(a) of the FD&C Act is categorically excluded and, therefore, normally does not require the preparation of an environmental assessment (EA) or 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 corresponding predicate tobacco products:

- Differences in tobacco blends (decrease in (b) (4) tobacco and increase in (b) (4) tobacco)
- Decrease in the amount of (b) (4) (15%-18%) and (b) (4) (30%)
- Addition of ingredients in the cigarette paper
- Increases and decrease of a number of ingredients
- Decrease (9%-10%) in tobacco rod density (SE0002701, SE0002704, SE0002708 and SE0002709)
- Increase (16%) in cigarette paper base paper basis weight (SE0002701, SE0002703-SE0002705, and SE0002708)
- Decrease (15%) in cigarette paper band porosity (SE0002700, SE0002702, and SE0002709)
- Decrease (14% - 17%) in total denier (SE0002701- SE0002703, SE0002705, SE0002706, and SE0002709)
- Decrease (11% - 22%) in denier per filament (SE0002700-SE0002706, SE0002708, and SE0002709)
- Decrease (9% - 15%) in filter pressure drop (SE0002701-SE0002706, and SE0002708)
- Decrease (18%) in filter ventilation (SE0002702 and SE0002705)
- Decrease (11%) in tobacco oven volatiles (moisture) (SE0002700–SE0002706, SE0002708, and SE0002709)
- Increase in NNK for SE0002703 (ISO: 37%; CI: 31%), SE0002708 (ISO: 28%), and SE0002709 (CI: 35%)
- Increase in filler cadmium for SE0002700 (36%), SE0002703 (26%), SE0002704 (25%), SE0002706 (24%), and SE0002709 (28%)
- Increase in Formaldehyde for SE0002700 (CI: 31%)

The applicant has failed to demonstrate that the following differences in characteristics do not cause the new tobacco products to raise different questions of public health. The applicant failed to provide arsenic and cadmium in the smoke given the large quantity of these metals in the tobacco filler and the amount of these metals can lead to higher smoke toxic metal levels and can cause the new tobacco products to raise different questions of public health. This was needed to establish exposure amounts to these metals in the smoke and also raised a concern from toxicology given the large amount of these metal found in the tobacco. The applicant used a surrogate new and a surrogate predicate tobacco product in lieu of measurements from the actual new and predicate tobacco product. The TPL has determined that the surrogate tobacco products could be used to bridge information to the new and predicate tobacco products accordingly as the applicant provided information that superseded previous information regarding the tobacco blend and ingredients that allowed a comparison to the new and predicate tobacco products. The applicant provided HPHCs for the new and predicate tobacco products; however, differences were identified that cause the new products to raise different questions of public health. Additionally, differences in ingredients were identified between the new and predicate tobacco products, many of which raise a toxicological concern for SE0002700, SE0002703, SE00002704, SE0002706, SE0002708, and SE0002709. A quantitative risk assessment (QRA) and probabilistic risk assessment (PRA) were provided, however, these assessments did not provide adequate information to determine that the differences in the ingredients and HPHCs do not cause the new products to raise different questions

of public health. Therefore, the applicant has failed to provide sufficient information to support a finding of substantial equivalence for these SE Reports.

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 chemistry, engineering, and toxicology reviews conclude that the new tobacco products have different characteristics 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. I do not concur in all aspects of the reviews, but still recommend that an NSE order letter be issued. Specifically, I did not concur that the surrogate tobacco products were not acceptable from chemistry. It was my assessment from the information provided in the latest amendment that the surrogate tobacco products could be used to bridge information to the new and predicate tobacco products as the applicant provided information that superseded previous information regarding the tobacco blend and ingredients that allowed a comparison to the new and predicate tobacco products. Additionally, I did not concur with the engineering review as our approach to certain engineering parameters has changed as outlined in the memo finalized on March 1, 2019.[7] The design parameters identified were not needed in this case and do not cause the new products to raise different questions of public health from the engineering perspective as an evaluation of changes in HPHC yields that may result from changes in design parameters are to be evaluated by chemistry and then evaluated by toxicology pending the methodology evaluation from chemistry.

Because the proposed action is issuing NSE orders, it is a class of action that is categorically excluded under 21 CFR 25.35(b). 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.

An NSE order letter should be issued for the new tobacco products in SE0002700-SE0002706, SE0002708, and SE0002709, as identified on the cover page of this review. The NSE order letter should cite the following deficiencies:

1. SE0002700 – SE0002706 and SE0002708 demonstrate higher tobacco cut filler cadmium and arsenic in one or more surrogate new tobacco products compared to the corresponding surrogate predicate tobacco products. However, your SE Reports do not include arsenic and cadmium smoke yields. Higher toxic metals levels in the tobacco cut filler can lead to higher smoke toxic metal levels and can cause the new tobacco products to raise different questions of public health. You needed to provide a rationale for why higher cut filler arsenic and cadmium do not cause the new tobacco products to raise different questions of public health. One way this issue could have been addressed is to provide the mainstream smoke yields of arsenic and cadmium for the surrogate new and surrogate predicate tobacco products under the ISO and Canadian Intense smoking regimens. If you would have collected this data, you would have needed to provide the following information about HPHC testing so that FDA can fully evaluate the HPHC data:

    a. Reference product datasets (e.g., 1R6F)

b. Quantitative test protocols and method used
c. Testing laboratory and their accreditation(s)
d. Length of time between date(s) of manufacture and date(s) of testing
e. Number of replicates
f. Standard deviation(s)
g. Complete data sets
h. A summary of the results for all testing performed
i. Storage conditions prior to initiating testing

2. SE0002700, SE0002704, SE0002706, and SE0002709 provide lists of the tobacco and ingredients added to the "Master Subject" and surrogate predicate products which represent the new and predicate products. You also provided HPHC values under the ISO and HCI smoking regimens for the Master Subject and corresponding surrogate predicate products. Based on the HPHC values you provided, CTP identified the following increases in filler and smoke yields from the Master Subject products when compared to the corresponding surrogate predicate products under the specified smoking regimens:

- SE0002700: Formaldehyde (CI: 31%); cadmium (filler: 36%)
- SE0002704: Cadmium (filler: 25%)
- SE0002706: Cadmium (filler: 24%)
- SE0002709: NNK (CI: 35%); cadmium (28%)

These HPHC increases can result from tobacco blend changes as well as ingredients added to tobacco and structural materials in the new products. The following ingredients that are added to or increased in the new products may contribute to the generation of HPHCs noted above when combusted:

a.
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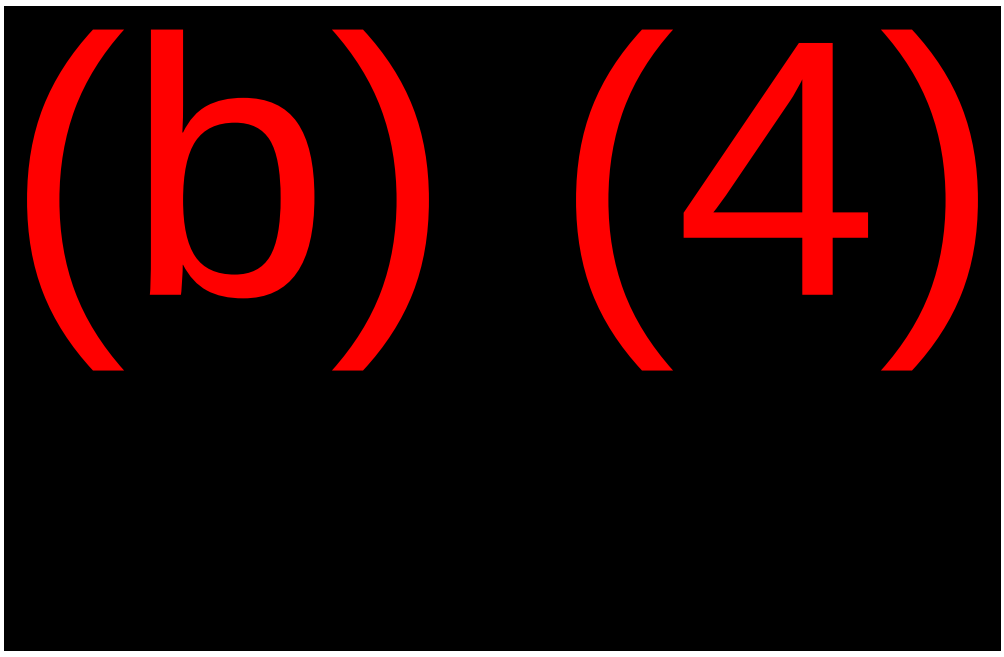

Exposures to the HPHCs listed above have been associated with cancer and noncancer adverse health effects. You voluntarily submitted quantitative risk assessments (QRAs) and probabilistic risk assessments (PRAs) to support your position that increases in HPHC levels as a result of tobacco blend and tobacco ingredient changes do not cause the new product to raise different questions of public health.

While a QRA/PRA is not required for an SE Report, such analyses can inform the review process if adequately described, supported with details and justifications. For FDA to review any risk assessment that is voluntarily provided in an application, you needed to submit a detailed account of the QRA, in line with recommendations from the National Academy of Sciences. In addition, you needed to provide all data, methods and a detailed description of the results and analysis of the QRA and PRA to demonstrate that user exposure to the Master subject products will not lead to increased toxicity or overall health risk compared to the corresponding surrogate predicate products would have been helpful. The data, results, and analysis of the QRAs and PRAs you provided are limited because they are either unclear or lack sufficient details.

a. You needed to provide specific evidence or rationale for the inclusion of body weight and daily inhalation rate in your exposure estimation regarding the smoker exposure scenario. In addition, you needed to provide clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime is appropriate for the specific products and expected user populations.

b. You needed to provide detailed selection criteria for the selection of all reference values and scientific evidence for deviating from established reference values. Including additional evidence or rationale for the selected reference values, given the availability of multiple reference values for a specific constituent. In addition, providing evidence that the reference values used in the calculation of the HQ or ILCR, in both the QRAs and PRAs, are appropriate for the toxicological endpoints associated with the use of the new and predicate products and for the expected product user populations.

c. You needed to provide a detailed description of how the calculated HQ or ICLR ratios between the respective new and predicate product (or surrogate new/surrogate predicate) HPHCs can be used to determine whether the new products raise different questions of public health.

d. In the 'Problem Formulation' section, you state that "*the risk assessment (i.e., QRA) presented herein does not concern absolute risk or hazard but rather the comparative risk or hazard between the two products.*" However, you provided data and a discussion relating to the absolute risk or hazard (e.g., the total cancer risk or

margin-of-exposure). You needed to provide clear description of how you intend to characterize and interpret the QRA and PRA results.

e. You needed to provide a complete description of the PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. You needed to provide scientific evidence and rationale demonstrating that the distributions for each parameter and the ranges are appropriate, given the characteristics of the new and predicate products and the anticipated user population of both products. You needed to consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions. Any rationale or scientific evidence needed to also include further discussion as to the quality and appropriateness of the inputs as well as the PRA expectations that the resulting parameter estimations accurately reflect the real product or user specific values.

Additionally, the submitted PRA, which relies on the same parameters in the QRA, the distributions and distribution parameters used in the exposure analyses were not adequately described. The current PRAs do not provide 1) the degree of certainty of risk estimates, 2) sufficient characterization of the uncertainty surrounding all critical elements of risk assessments, 3) insight regarding how the risk estimates vary among different percentiles of an exposed population, including sensitive populations or life stages, and 4) description of the key contributors to variability or uncertainty in predicted exposures or risk estimates. You conducted simulations using distributions for population and behavioral parameters, such as cigarettes per day (CpD) and inhalation rates. This type of analysis is useful in examining what factors may impact an individual smoker's risk the most, as noted in your sensitivity analyses. You needed to provide scientific evidence and rationale demonstrating that the distributions for each parameter and the ranges are appropriate given the characteristics of the new and predicate products and the anticipated user population of both products. Any rationale or scientific evidence needed to include discussion as to the quality and appropriateness of the inputs as well as the PRA expectations that the resulting estimations accurately reflect the new and predicate specific values. For example, the distribution of cigarettes per day is listed as 1-95, but you did not provide specific data or rationale showing this is a representative range for the "Master Subject" product or surrogate predicate products. This example is particularly important as it is, according to sensitivity analyses, the biggest driver of variability. Additionally, you did not specify if results of the cumulative ILCR and HI are based on mean estimated values or across a distribution, which would allow for comparisons across a range of percentiles. Comparisons of upper percentiles (e.g. 90th or 95^{th} percentiles), for example, may likely better capture the potential differences in health risks for users that may occur. In SE0002700, the smoke yield of carcinogenic formaldehyde was increased in the "Master Subject" product beyond the analytically equivalent levels under the HCI smoking condition; and carcinogenic NNK was increased beyond analytically equivalent levels in the Master Subject products described in SE0002700, SE0002704, SE0002706, and SE0002709 which

contributes to an increase in cancer risk from cigarette which exceeds the estimated risk for surrogate predicate products. You needed to provide scientific evidence and a rationale that the HPHC increases associated with tobacco blend and ingredient changes in SE0002700, SE0002704, SE0002706, and SE0002709 do not cause the new products to raise different questions of public health.

3. SE0002703 and SE0002708 provide lists of the tobacco and ingredients added to the "Master Subject" and surrogate predicate products which represent the new and predicate products. You also provided HPHC values under the ISO and HCI smoking. Based on the HPHC values you provided, CTP identified the following increases in filler and smoke yields from the Master Subject products when compared to the corresponding surrogate predicate products under the specified smoking regimens:

   - SE0002703: NNK (ISO: 37%; CI: 31%); cadmium (filler: 26%)
   - SE0002708: NNK (ISO: 28%)

   These HPHC increases can result from tobacco blend changes as well as ingredients added to tobacco and structural materials in the new products. The following ingredients that are added to or increased in the new products may contribute to the generation of HPHCs noted abov

   a.
   b.
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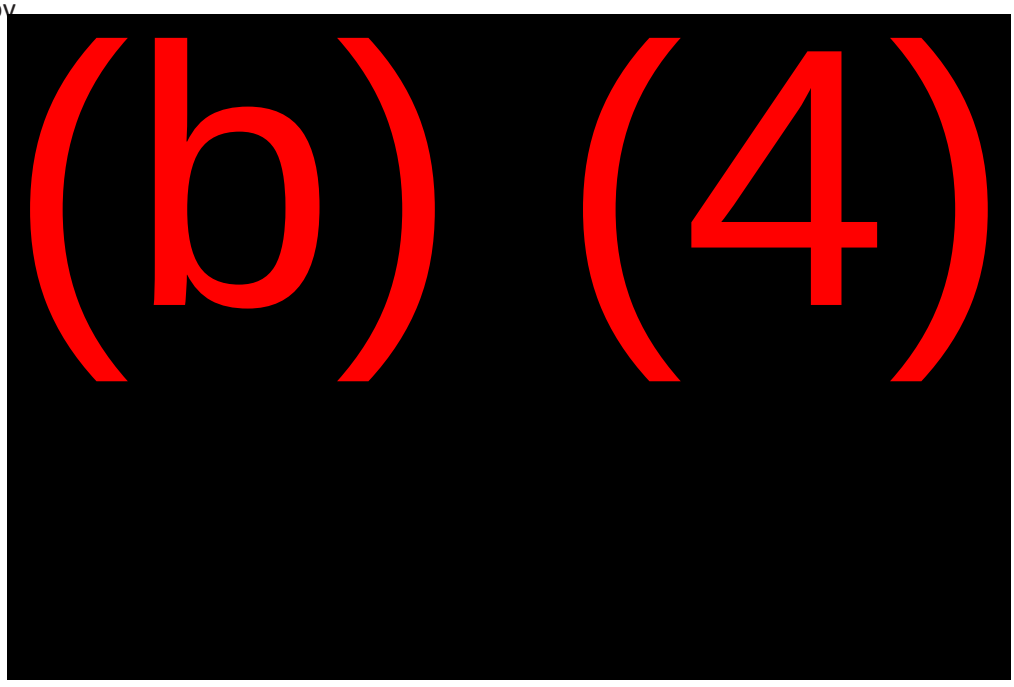

You voluntarily submitted quantitative risk assessments (QRAs) and probabilistic risk assessments (PRAs) to support your position that increases in HPHC levels as a result of tobacco blend and tobacco ingredient changes do not cause the new product to raise different questions of public health. However, a risk assessment approach is unlikely to demonstrate that the new products in these SE Reports do not raise different questions of public health because there are

only HPHC increases and no concomitant HPHC decreases compared to the surrogate predicate product and therefore there are no decreased risks that could offset the cancer risk and noncancer hazard associated with the HPHC increases associated with the new product. You needed to provide scientific evidence and a rationale that the HPHC increases associated with tobacco blend and ingredient changes in SE0002703 and SE0002708 do not cause the new products to raise different questions of public health.