FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review: SE0006198, SE0006199, and SE0006211

SE0006198: GPC Silver 100's Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	98 mm
Diameter	7.8 mm
Ventilation	53%
Characterizing Flavor	None
SE0006199: GPC Silver Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Ventilation	59%
Characterizing Flavor	None
SE0006211: Kamel Red Smooth Taste Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Ventilation	25%
Characterizing Flavor	None
Common Attributes of SE Reports	
Applicant	R.J. Reynolds Tobacco Company
Report Type	Provisional
Product Category	Cigarette
Product Sub-Category	Filtered Combusted
Recommendation	
Issue a Not Substantially Equivalent (NSE) Order.	

Technical Project Lead (TPL):

Matthew J. Walters -S
2018.05.03 13:17:44 -04'00'

Matthew J. Walters, Ph.D., MPH
CDR, US 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: 2018.05.03 14:13:18 -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:

SE0006198: GPC Silver 100's Box	
Product Name	GPC Ultra Light 100s Box
Package Type	Box
Package Quantity	20 cigarettes
Length	98 mm
Diameter	7.8 mm
Ventilation	52%
Characterizing Flavor	None
SE0006199: GPC Silver Box	
Product Name	GPC Ultra Light King Box
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Ventilation	52%
Characterizing Flavor	None
SE0006211: Kamel Red Smooth Taste Box	
Product Name	Red Kamel Lights
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.8 mm
Ventilation	32%
Characterizing Flavor	None

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

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

FDA received the SE Reports on March 22, 2011 and issued Acknowledgement letters on March 25, 2013. On March 21, 2013, FDA received an amendment (SE0007894) from the applicant to request additional time to respond to anticipated[1] Advice/Information Request (A/I) letters for the SE Reports. FDA issued A/I letters on March 25, 2013. On April 1, April 5, April 9, and April 11, 2013, FDA conducted teleconferences to discuss the applicant's timeline and proposal to amend the SE Reports in response to the March 25, 2013 A/I letter. On April 11, 2013, FDA received the applicant's timeline and proposal to amend the SE Reports (SE0008212). FDA issued an Extension Response letter on April 17, 2013 requesting the applicant submit a complete response to the A/I letters and any additional information

[1] The applicant had received A/I letters for other SE Reports not subject to this review. In anticipation of receipt of similar A/I letters for the SE Reports subject of this review, RAIS proactively requested an extension of time.

prior to the start of scientific review[2] of the SE Reports. On February 20, 2013, FDA completed Public Health Impact (PHI) reviews for the SE Reports, and assigned the reports to PHI Tier 1 based on insufficient information to determine whether other PHI tiers were more appropriate. FDA issued an A/I letter on May 10, 2013, to request additional information from the applicant to assist FDA with assessing the appropriate PHI tier to place the SE Reports. On July 9, 2013, FDA received the applicant's response to the A/I letter (SE0009249, SE0009255, and SE0009224). A detailed review of the product composition information in the amendments prompted FDA to reassign all of the SE Reports to PHI Tier 2. FDA issued a Notification letter on October 13, 2015 stating that FDA intends to begin scientific review of the SE Reports on November 27, 2015. The Notification Letter erroneously included SE Reports that had completed a transfer of ownership to a different manufacturer. On October 20, 2015, FDA received an unsolicited amendment (SE0012511) from the applicant, clarifying that due to the transfer of ownership of certain brands to ITG Brands, LLC, the applicant intended to provide amendments for only those SE Reports for which it remained the applicant of record. On November 25, 2015, FDA received amendments (SE0012695, SE0012696, and SE0012698) to the SE Reports from the applicant. FDA issued a Preliminary Finding (PFind) letter on March 18, 2016. On April 15, 2016, FDA received the applicant's response to the PFind letter (SE0013308), which included the applicant's request for a claim of categorical exclusion for all three SE Reports. FDA issued an A/I letter on September 21, 2016. On November 9, 2016, FDA conducted a teleconference to provide a response to the applicant's clarifying questions for the A/I letter. On November 18, 2016, FDA received the applicant's response to the A/I letter (SE0013753). FDA issued a PFind letter on June 29, 2017. The due date of the response to the PFind letter was July 29, 2017. On July 5, 2017, FDA received an extension request from the applicant (SE0014193). The applicant requested six additional months to respond to the Pfind letter, so that it could first conduct literature reviews and analytical research and then use this information to conduct risk assessments of identified ingredient(s) and/or their pyrolysis products. FDA issued an Extension Granted letter on July 26, 2017. The due date of response to the Pfind letter was extended to January 5, 2018. On January 5, 2018, FDA received the applicant's response to the PFind letter (SE0014460).

Product Name	SE Report	Amendments
GPC Silver 100's Box	SE0006198	SE0007894 SE0008212 SE0009249 SE0012511 SE0012696 SE0013308 SE0013753 SE0014193 SE0014460
GPC Silver Box	SE0006199	SE0007894 SE0008212 SE0009255 SE0012511 SE0012695

[2] FDA stated in this letter that, at a later date, it would issue a letter notifying RAIS of the projected scientific review start date of the SE Reports.

Product Name	SE Report	Amendments
		SE0013308 SE0013753 SE0014193 SE0014460
Kamel Red Smooth Taste Box	SE0006211	SE0007894 SE0008212 SE0009224 SE0012511 SE0012698 SE0013308 SE0013753 SE0014193 SE0014460

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 Marcella White on March 25, 2013 and by Jennifer Schmitz on February 28, 2018.

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 review dated May 8, 2016 concluded 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.[3]

4. SCIENTIFIC REVIEW

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

[3] Addendum reviews were completed on March 30, 2018, to clarify the package type and size for the predicate and new tobacco products. Since the initial grandfather determination on May 8, 2016, was based on a product of that package type and size, the addendum reviews do not change the conclusion of the initial determination.

4.1. CHEMISTRY

Chemistry reviews were completed by Megan Mekoli on July 29, 2016, January 24, 2017 and March 2, 2018.

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

SE0006198:

- The new product contains 78% more (b) (4), 52% more (b) (4), and 13% more (b) (4) than the predicate product.
- The new product contains 13% more (b) (4) in the tobacco mixture than the predicate product.
- The new product contains 10% more formaldehyde in mainstream smoke under the CI smoking regimen than the predicate product.

SE0006199:

- The new product contains 51% more (b) (4), 13% more (b) (4), and 29% more (b) (4) than the predicate product.
- The new product contains 13% more (b) (4) in the tobacco mixture than the predicate product.
- The new product contains 40% more formaldehyde in mainstream smoke under the CI smoking regimen than the predicate product.

SE0006211:

- The new product contains 189% more (b) (4), 19% more (b) (4), and 6% more (b) (4) than the predicate product.
- The new product contains 8% greater (b) (4) and 26% more (b) (4) than the predicate product.
- The new product contains (b) (4) that is absent in the predicate product.
- The new product contains 20% greater formaldehyde in mainstream smoke under ISO smoking regimen than the predicate product.

The applicant provided the quantities of all tobaccos within the tobacco blends and ingredients for the new and corresponding predicate products. The new products contained greater quantities of (b) (4) (SE0006198 & SE0006211), (b) (4) (SE0006199), (b) (4) (SE0006198 & SE0006199), (b) (4) (SE0006211), and (b) (4) (all the SE Reports) tobaccos as well as increased quantities of (b) (4) (SE0006198 & SE0006199; included in (b) (4)) than the corresponding predicate products. To address these increased quantities of tobaccos and (b) (4) as well as the increases in (b) (4) (SE0006211) and (b) (4) (SE0006211), the applicant provided quantities of tar, nicotine, and carbon monoxide (TNCO), acetaldehyde, acrolein, formaldehyde, and benzo[a]pyrene (B[a]P) in the mainstream smoke under ISO and CI smoking conditions of the new and corresponding predicate products. The applicant also provided measurements of TSNAs (such as NNN and NNK), NOx, benzene, and other volatile organic carbons (VOCs) such as toluene and 1,3-

butadiene in the mainstream smoke under ISO and CI smoking conditions, of all the new and the corresponding predicate products to address the differences in tobacco blend and ingredients. The quantities of NNN, NNK, NOx, benzene, and other VOCs for the new products were found to be lower or equivalent to those of the corresponding predicate products within the analytical performance of the reported methods. While the quantities of acrolein and acetaldehyde were lower or equivalent and were within the expected variability of the analytical methods between the new and corresponding predicate products, the quantity of formaldehyde in mainstream smoke under ISO and CI smoking regimens was 10% - 40% ([redacted] (b) (4)) greater in the new products. Chemistry has deferred these increases in formaldehyde to toxicology for further examination. Chemistry further determined that the applicant has provided sufficient testing information such as analytical methods, testing conditions, number of replicates, raw data, standard results, accreditation of the laboratory, and dates of manufacture and testing. Therefore, the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a chemistry perspective.

4.2. ENGINEERING

Engineering reviews were completed by James Cheng on July 8, 2016 and January 17, 2017.

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

- Changes in the base paper basis weight, base paper porosity, band porosity, and ventilation.

The new products have a similar or lower tobacco filler mass than the corresponding predicate products. The applicant indicated that they use multiple materials for components such as the cigarette paper, adhesives and plug wrap, and, in its initial submission, provided design specifications for these components that were composites of the values for the multiple materials. However, the applicant then withdrew the use of multiple materials and specified single materials for all components and as such, the applicant has provided updated design specifications and test data for the new products that reflect the use of single material components. These single materials of the new products were nearly identical to the components of the corresponding predicate tobacco products with only minor differences in the base paper basis weight, base paper porosity, band porosity, and ventilation. The applicant also provided valid updated TNCO testing for the new products that have been reformulated to use single material components, which showed minimal differences in TNCO yields between the new and corresponding predicate products. The TNCO testing is used to evaluate any differences in product design features from the engineering perspective. Therefore, the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from an engineering perspective.

4.3. TOXICOLOGY

Toxicology reviews were completed by James Hobson on September 9, 2016, Anna Depina on June 20, 2017, and Kausar Riaz Ahmed on March 1, 2018.

The final toxicology review 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. The review identifies the following deficiency that has *not* been adequately resolved:

1. All of your SE Reports indicate statistically significant increase in formaldehyde levels in the new products compared to the corresponding predicate products. Formaldehyde is a carcinogen and a respiratory toxicant. The ingredients, (b) (4) and (b) (4), that are increased in the new products as compared to the predicate products, can produce formaldehyde upon pyrolysis. You provided individual constituent and composite quantitative risk assessment (QRA) and a probabilistic risk assessment (PRA) as supporting evidence that HPHC changes between the new and predicate products do not cause the new products to raise different questions of public health. While a QRA/PRA is not required for an SE Report, it can inform the substantial equivalence determination. However, the submitted QRA/PRA, in its present form, is insufficient to support the position that the increase in formaldehyde does not cause the new products to raise different questions of public health. Several issues were identified with the QRA/PRA approach you presented. Specifically, these include:

   QRA

   Hazard Identification:

   A more comprehensive QRA is required to effectively compare the risks of the new product relative to the predicate product. For SE0006198, the QRA did not include acetaldehyde, although there are small increases in smoke yields of this HPHC from new product as compared to the corresponding predicate product. This selective use of HPHCs in the QRA calculations may introduce bias in the assessment of cancer and noncancer effects associated with exposure to the new and predicate products. In the context of evaluating differences between the new and predicate products in these SE Reports, the Hazard ID section of the QRA should consider all the HPHCs that can inform whether the differences in product characteristics between the new and predicate products may cause the new products to raise different questions of public health. Provide evidence that the HPHCs measured and considered in the QRA are representative of the relative cumulative risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, all measured HPHCs should be included in the QRA.

   Hazard Characterization

   You used toxicity values developed by CalEPA for acetaldehyde and formaldehyde, and values developed Texas Commission for Environmental Quality (TCEQ) for acrolein and 1,3-butadiene. However, toxicity values for these compounds have also been developed by the U.S.EPA Integrated Risk Information System (EPA IRIS). Specifically, EPA IRIS reference concentrations (RfCs) have been published for acetaldehyde, acrolein and 1,3-

butadiene; IURs were developed by EPA IRIS for acetaldehyde, 1,3-butadiene and formaldehyde. The toxicity values used may have a significant impact on the result of the risk assessment. In general, the EPA IRIS toxicity values are developed using the best available science, are transparent about the data and methodologies used, and undergo a rigorous peer review process. Provide information and a rationale demonstrating why the CalEPA and TCEQ toxicity values are more appropriate than the toxicity values developed by EPA IRIS, for the evaluation of non- cancer hazard and cancer risks associated with inhalation exposures to these HPHCs.

NNN and NNK: For NNN and NNK, you developed IURs using route-to-route extrapolation from their respective oral cancer slope factors (CSF). You assert that "absorption, metabolism, and distribution following oral and inhalation routes are equivalent." However, you did not provide evidence to substantiate this claim. Provide information relevant to the toxicokinetics and toxicodynamics for NNN and NNK via the oral and inhalation routes, to demonstrate that the methods and assumptions used for the route-to-route extrapolations are appropriate. In addition, the following issues were identified with the CSFs you proposed for NNN and NNK:

NNN *Cancer slope factor:* You proposed an oral CSF of 0.83 per mg/kg/d for NNN. You use this oral CSF in the QRA to develop an IUR of 2.4E-04 (µg/m3)-1. You calculated the proposed CSF by applying a factor of 0.59 to the CSF of 1.4 per mg/kg/d developed by OEHHA. You assert that your proposed CSF was developed using the U.S. EPA recommended cross-species scaling factor of (BW3/4) and thus used a more current cross-species scaling factor for the study administered dose than OEHHA. However, the cross-species scaling factor (BW3/4) should be used to estimate the human equivalent dose (HED) from the animal data, and should not be used to adjust an already developed CSF. For this reason, the method used to develop the proposed oral CSF for NNN is not considered appropriate.

NNK *Cancer slope factor*: You proposed an oral CSF for NNK of 19 per mg/kg/d. You use this oral CSF in the QRA to develop an IUR of 5.2E-03 (µg/m3)-1. You calculated the proposed oral CSF using the BMDL10 calculated by Naufal et al. (2009) for lung tumor data published in the NNK oral exposure study by Rivenson et al. (1988). However, the evaluation by Naufal et al. (2009) indicates that NNK oral exposures resulted in increased tumors in the lung, pancreas, liver and nasal cavity. The study by Riverson et al., 1998[4] was also used by OEHHA to develop the CSF for NNK of 49 mg/kg/day; this value considered the increased tumor incidence across all tissues (i.e., lung, pancreas, liver, and nasal cavity). You did not provide data or scientific evidence to demonstrate that the proposed

[4] The 3rd toxicology review dated March 1, 2018 contained an error with the identification of the reference. This should have been Rivenson et al., 1988. This has been corrected in the letter ready comments.

CSF for NNK of 19 per mg/kg/d is more appropriate to estimate the upper-bound excess lifetime cancer risk for NNK exposure than the NNK CSF of 49 mg/kg/day (OEHHA 2001).

When deriving cancer potency factors, provide more detailed information about the rationale for the calculations of IURs, including all details on route-to-route extrapolations, dose response modelling, and statistical frameworks.

Risk Characterization
As discussed above, several issues were identified with the data inputs used for the risk characterization (e.g., HPHCs considered in the evaluation and toxicity values). For these reasons, the data, information and conclusions provided in the risk characterization were not considered adequately representative of the potential differences in non-cancer hazard and cancer risk between the new and predicate products in these SE Reports.

PRA
You provided a probabilistic risk assessments (PRA) for the same HPHCs included in the QRA, and therefore, all the limitations of the QRA also apply to the PRA. In addition, although the assumed minimum, maximum and mean values for the distributions are provided, no justifications for the selected distributions are supplied, and the values selected for the parameters have several limitations that may restrict the applicability of the PRA, including:

a. *Cigarettes per day (CpD):* For the CpD, you used CpD, and average of 15.98 CpD. You state that "*every day smokers smoked between 0 and 100 cigarettes per day, with an average value of 15.98 cigarettes per day*", citing the MMWR report from CDC (2014); this report seems to be incorrectly referenced in the text as CDC (2015). The report by CDC shows that among adult daily smokers, 40.3% smoked 10-19 CpD; 29.3% smoked 20-29 CpD; 23.3% smoked 1-9 CpD; and, 7.1% smoked ≥30 CpD. This data does not support the CpD range, and minimum of 0.03 you used in the PRA for "every day smokers". In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

b. *Exposure duration (ED):* For the exposure duration, you indicate using a BetaPERT distribution with a range from 6 months to 73 years, an average ED of 20.3 years. You state that "*application of NHANES questionnaire data suggest that the duration of smoking ranged from 7 to 73 years, with a mean duration of 20.3 years*." These data indicate a minimum ED of 7 years, and do not support the minimum ED of 6 months used in your PRA. In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

c. *Daily inhalation rate (DIR):* For the DIR, you used a BetaPERT distribution with a rage of 6.24 m3/day to 23.26 m3/day, and average of 13.51 m3/day, references the US EPA Exposure Factors Handbook (USEPA 2011), table 6.4. The USEPA 2011 Exposure Factors Handbook provides inhalation rates for females, males, and combined (males and females) for different age groups, and could be used to obtain the best distribution fit on the data. You did not provide a rationale for using a BetaPERT distribution for the inhalation rate. Also, you did not provide a scientific rationale and

evidence for how the use of the selected inhalation rates are appropriate for tobacco use exposure scenario.

Provide evidence that the HPHCs considered in the PRA are representative of the relative composite risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, the PRA should include all measured HPHCs from the new and predicate products.

In conclusion, provide sufficient data and a detailed description of the results and analysis of the QRA/PRA to demonstrate that user exposure to the new product will not lead to increased toxicity or overall health risk when compared to the predicate product. For PRA, provide a complete description of the design of the assessment or simulations such that it informs the comparison of health risks between the new and predicate products. If distributions are to be used in a PRA, select parameters that could provide insight into such a comparison of health risks. For example, distributions around parameters that differ between the products are more informative than distributions around population variables which should be the same between products. Finally, for all SE Reports provide sufficient scientific evidence and a rationale to demonstrate that increase in formaldehyde levels in the new products, compared to the predicate products, does not cause the new products to raise different questions of public health.

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

4.4. SOCIAL SCIENCE

Social science reviews were completed by Elisabeth Sherman on January 27, 2017.

The final social science 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 social science perspective. Therefore, the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health 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 differences in characteristics between the new and corresponding predicate tobacco products:

- SE0006198:
  - The new product contains 78% more (b) (4), 52% more (b) (4), and 13% more (b) (4) than the predicate product.
  - The new product contains 13% more (b) (4) in the tobacco mixture than the predicate product.
  - The new product contains 98% ((b) (4)) more (b) (4) in the cigarette paper than the predicate product.
  - The new tobacco contains (b) (4) in the tobacco filler whereas the predicate tobacco product does not contain this ingredient.[5]
  - The new product contains 10% more formaldehyde in mainstream smoke under the CI smoking regimen than the predicate product.
  - Changes in the base paper basis weight, base paper porosity, band porosity, and ventilation.
- SE0006199:
  - The new product contains 51% more (b) (4), 13% more (b) (4), and 29% more (b) (4) than the predicate product.
  - The new product contains 13% more (b) (4) in the tobacco mixture than the predicate product.
  - The new product contains 99% ((b) (4)) more (b) (4) in the cigarette paper than the predicate product.
  - The new tobacco contains (b) (4)) in the tobacco filler whereas the predicate tobacco product does not contain this ingredient.[5]
  - The new product contains 40% more formaldehyde in mainstream smoke under the CI smoking regimen than the predicate product.
  - Changes in the base paper basis weight, base paper porosity, band porosity, and ventilation.
- SE0006211:
  - The new product contains 189% more (b) (4), 19% more (b) (4), and 6% more (b) (4) than the predicate product.
  - The new product contains 8% greater (b) (4)) and 26% (b) (4) more (b) (4) than the predicate product.
  - The new product contains (b) (4) that is absent in the predicate product.
  - The new product contains 20% greater formaldehyde in mainstream smoke under ISO smoking regimen than the predicate product.
  - Changes in the base paper basis weight, base paper porosity, band porosity, and ventilation.

The applicant has failed to demonstrate that the following difference in characteristics does not cause the new tobacco products to raise different questions of public health. For all SE Reports,

[5] While the final toxicology review does not explicitly address whether the applicant had provided adequate evidence whether this ingredient causes the new product to raise different questions of public health, I have determined, as TPL, that this this ingredient is at a low concentration that does not cause the new product to raise different questions of public health.

there are analytically measurable increases in formaldehyde levels in the new products compared to the corresponding predicate products. The applicant submitted individual constituent and composite quantitative risk assessment (QRA) and probabilistic risk assessment (PRA) as supporting evidence that the HPHC differences between the new and corresponding predicate products do not cause the new products to raise different questions of public health. However, several issues were identified and the QRA/PRA was insufficient to support the claim that the increase in formaldehyde does 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.

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 toxicology review concludes 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 concur with this review and recommend that NSE order letters be issued.

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 determine that none exist. Therefore, the proposed action does not require preparation of an environmental assessment or an environmental impact statement.

NSE order letters should be issued for the new tobacco products in SE0006198, SE0006199, SE0006211 as identified on the cover page of this review.

6.1. DEFICIENCIES FOR SE0006198

A NSE order letter for SE0006198 should cite the following deficiency:

1. Your SE Report indicates a statistically significant increase in formaldehyde level in the new product compared to the predicate product. Formaldehyde is a carcinogen and a respiratory toxicant. The ingredient (b) (4) [redacted], increased in the new product as compared to the predicate product, can produce formaldehyde upon pyrolysis. You provided an individual constituent and composite quantitative risk assessment (QRA) and a probabilistic risk assessment (PRA) as supporting evidence that HPHC changes between the new and predicate product does not cause the new product to raise different questions of public health. While a QRA/PRA is not required for an SE Report, it can inform the substantial equivalence determination. However, the submitted QRA/PRA, in its present form, is insufficient to support the position that the increase in formaldehyde does not cause the new product to raise different questions of public health. Several issues were identified with the QRA/PRA approach you presented. Specifically, these include:

QRA

Hazard Identification:

A more comprehensive QRA is required to effectively compare the risks of the new product relative to the predicate product. The QRA did not include acetaldehyde, although there are increases in smoke yields of this HPHC in the new product relative to the predicate product. This selective use of HPHCs in the QRA calculations may introduce bias in the assessment of cancer and noncancer effects associated with exposure to the new and predicate products. In the context of evaluating differences between the new and predicate products in this SE Report, the Hazard identification section of the QRA should consider all the HPHCs that can inform whether the differences in product characteristics between the new and predicate products may cause the new product to raise different questions of public health. You needed to provide evidence that the HPHCs measured and considered in the QRA are representative of the relative cumulative risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, all measured HPHCs should be included in the QRA.

Hazard Characterization

You used toxicity values developed by CalEPA for acetaldehyde and formaldehyde, and values developed by Texas Commission for Environmental Quality (TCEQ) for acrolein and 1,3-butadiene. However, toxicity values for these compounds have also been developed by the U.S.EPA Integrated Risk Information System (EPA IRIS). Specifically, EPA IRIS reference concentrations (RfCs) have been published for acetaldehyde, acrolein and 1,3-butadiene; IURs were developed by EPA IRIS for acetaldehyde, 1,3-butadiene and formaldehyde. The toxicity values used may have a significant impact on the result of the risk assessment. In general, the EPA IRIS toxicity values are developed using the best available science, are transparent about the data and methodologies used, and undergo a rigorous peer review process. You needed to provide information and a rationale demonstrating why the CalEPA and TCEQ toxicity values are more appropriate than the toxicity values developed by EPA IRIS, for the evaluation of noncancer hazard and cancer risks associated with inhalation exposures to these HPHCs.

NNN and NNK: For NNN and NNK, you developed IURs using route-to-route extrapolation from their respective oral cancer slope factors (CSF). You assert that “absorption, metabolism, and distribution following oral and inhalation routes are equivalent.” However, you did not provide evidence to substantiate this claim. You needed to provide information relevant to the toxicokinetics and toxicodynamics for NNN and NNK via the oral and inhalation routes, to demonstrate that the methods and assumptions used for the route-to-route extrapolations are appropriate. In addition, the following issues were identified with the CSFs you proposed for NNN and NNK:

NNN *Cancer slope factor:* You proposed an oral CSF of 0.83 per mg/kg/d for NNN. You use this oral CSF in the QRA to develop an IUR of 2.4E-04 (µg/m3)-1. You calculated the proposed CSF by applying a factor of 0.59 to the CSF of 1.4 per mg/kg/d developed by OEHHA. You state that your proposed CSF was developed using the U.S. EPA recommended cross-species scaling factor of (BW3/4) and thus used a more current cross-species scaling factor for the study administered dose than OEHHA. However, the cross-species scaling factor (BW3/4) should be used to estimate the human equivalent dose (HED) from the

animal data, and should not be used to adjust an already developed CSF. For this reason, the method used to develop the proposed oral CSF for NNN is not considered appropriate.

NNK *Cancer slope factor*: You proposed an oral CSF for NNK of 19 per mg/kg/d. You use this oral CSF in the QRA to develop an IUR of 5.2E-03 (µg/m3)-1. You calculated the proposed oral CSF using the BMDL10 calculated by Naufal et al. (2009) for lung tumor data published in the NNK oral exposure study by Rivenson et al. (1988). However, the evaluation by Naufal et al. (2009) indicates that NNK oral exposures resulted in increased tumors in the lung, pancreas, liver and nasal cavity. The study by Riverson et al., 1988 was also used by OEHHA to develop the CSF for NNK of 49 mg/kg/day; this value considered the increased tumor incidence across all tissues (i.e., lung, pancreas, liver, and nasal cavity). You needed to provide data or scientific evidence to demonstrate that the proposed CSF for NNK of 19 per mg/kg/d is more appropriate to estimate the upper-bound excess lifetime cancer risk for NNK exposure than the NNK CSF of 49 mg/kg/day (OEHHA 2001).

When deriving cancer potency factors, you needed to provide more detailed information about the rationale for the calculations of IURs, including all details on route-to-route extrapolations, dose response modelling, and statistical frameworks.

Risk Characterization
As discussed above, several issues were identified with the data inputs used for the risk characterization (e.g., HPHCs considered in the evaluation and toxicity values). For these reasons, the data, information and conclusions provided in the risk characterization were not considered adequately representative of the potential differences in non-cancer hazard and cancer risk between the new and predicate products.

PRA
You provided a probabilistic risk assessment (PRA) for the same HPHCs included in the QRA, and therefore, all the limitations of the QRA also apply to the PRA. In addition, although the assumed minimum, maximum and mean values for the distributions are provided, no justifications for the selected distributions are supplied, and the values selected for the parameters have several limitations that may restrict the applicability of the PRA, including:

a. *Cigarettes per day (CpD):* For the CpD, you used a BetaPERT distribution with a range of 0.03-100 CpD, and an average of 15.98 CpD. You state that, "*every day smokers smoked between 0 and 100 cigarettes per day, with an average value of 15.98 cigarettes per day*", citing the MMWR report from CDC (2014); this report seems to be incorrectly referenced in the text as CDC (2015). The report by CDC shows that among adult daily smokers, 40.3% smoked 10-19 CpD; 29.3% smoked 20-29 CpD; 23.3% smoked 1-9 CpD; and, 7.1% smoked ≥30 CpD. This data does not support the CpD range, and minimum of 0.03 you used in the PRA for "every day smokers". In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

b. *Exposure duration (ED):* For the exposure duration, you indicate using a BetaPERT distribution with a range from 6 months to 73 years, an average ED of 20.3 years. You state that, "*application of NHANES questionnaire data suggest that the duration of smoking ranged from 7 to 73 years, with a mean duration of 20.3 years*." These data

indicate a minimum ED of 7 years, and do not support the minimum ED of 6 months used in your PRA. In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

c. *Daily inhalation rate (DIR):* For the DIR, you used a BetaPERT distribution with a range of 6.24 m^3/day to 23.26 m^3/day, and average of 13.51 m^3/day, references the US EPA Exposure Factors Handbook (USEPA 2011), table 6.4. The USEPA 2011 Exposure Factors Handbook provides inhalation rates for females, males, and combined (males and females) for different age groups, and could be used to obtain the best distribution fit on the data. You did not provide a rationale for using a BetaPERT distribution for the inhalation rate. Also, you did not provide a scientific rationale and evidence for how the use of the selected inhalation rates are appropriate for tobacco use exposure scenario.

You needed to provide evidence that the HPHCs considered in the PRA are representative of the relative composite risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, the PRA needed to include all measured HPHCs from the new and predicate products.

In conclusion, you needed to provide sufficient data and a detailed description of the results and analysis of the QRA/PRA to demonstrate that user exposure to the new product will not lead to increased toxicity or overall health risk when compared to the predicate product. For the PRA, you needed to provide a complete description of the design of the assessment or simulations such that it informs the comparison of health risks between the new and predicate products. If distributions are to be used in a PRA, you needed to provide select parameters that could provide insight into such a comparison of health risks. For example, distributions around parameters that differ between the product are more informative than distributions around population variables which should be the same between products. Finally, you needed to provide sufficient scientific evidence and a rationale to demonstrate that increase in formaldehyde levels in the new product compared to the predicate product does not cause the new product to raise different questions of public health.

6.2. DEFICIENCIES FOR SE0006199

A NSE order letter for SE0006199 should cite the following deficiency:

1. Your SE Report indicates a statistically significant increase in formaldehyde level in the new product compared to the predicate product. Formaldehyde is a carcinogen and a respiratory toxicant. The ingredient (b) (4) [redacted], increased in the new product as compared to the predicate product, can produce formaldehyde upon pyrolysis. You provided an individual constituent and composite quantitative risk assessment (QRA) and a probabilistic risk assessment (PRA) as supporting evidence that HPHC changes between the new and predicate product does not cause the new product to raise different questions of public health. While a QRA/PRA is not required for an SE Report, it can inform the substantial equivalence determination. However, the submitted QRA/PRA, in its present form, is insufficient to support the position that the increase in formaldehyde does not cause the

new product to raise different questions of public health. Several issues were identified with the QRA/PRA approach you presented. Specifically, these include:

QRA

Hazard Identification:

A more comprehensive QRA is required to effectively compare the risks of the new product relative to the predicate product. The QRA did not include acetaldehyde, although there are increases in smoke yields of this HPHC in the new product relative to the predicate product. This selective use of HPHCs in the QRA calculations may introduce bias in the assessment of cancer and noncancer effects associated with exposure to the new and predicate products. In the context of evaluating differences between the new and predicate products in this SE Report, the Hazard identification section of the QRA should consider all the HPHCs that can inform whether the differences in product characteristics between the new and predicate products may cause the new product to raise different questions of public health. You needed to provide evidence that the HPHCs measured and considered in the QRA are representative of the relative cumulative risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, all measured HPHCs should be included in the QRA.

Hazard Characterization

You used toxicity values developed by CalEPA for acetaldehyde and formaldehyde, and values developed by Texas Commission for Environmental Quality (TCEQ) for acrolein and 1,3-butadiene. However, toxicity values for these compounds have also been developed by the U.S.EPA Integrated Risk Information System (EPA IRIS). Specifically, EPA IRIS reference concentrations (RfCs) have been published for acetaldehyde, acrolein and 1,3-butadiene; IURs were developed by EPA IRIS for acetaldehyde, 1,3-butadiene and formaldehyde. The toxicity values used may have a significant impact on the result of the risk assessment. In general, the EPA IRIS toxicity values are developed using the best available science, are transparent about the data and methodologies used, and undergo a rigorous peer review process. You needed to provide information and a rationale demonstrating why the CalEPA and TCEQ toxicity values are more appropriate than the toxicity values developed by EPA IRIS, for the evaluation of noncancer hazard and cancer risks associated with inhalation exposures to these HPHCs.

NNN and NNK: For NNN and NNK, you developed IURs using route-to-route extrapolation from their respective oral cancer slope factors (CSF). You assert that “absorption, metabolism, and distribution following oral and inhalation routes are equivalent.” However, you did not provide evidence to substantiate this claim. You needed to provide information relevant to the toxicokinetics and toxicodynamics for NNN and NNK via the oral and inhalation routes, to demonstrate that the methods and assumptions used for the route-to-route extrapolations are appropriate. In addition, the following issues were identified with the CSFs you proposed for NNN and NNK:

NNN *Cancer slope factor:* You proposed an oral CSF of 0.83 per mg/kg/d for NNN. You use this oral CSF in the QRA to develop an IUR of 2.4E-04 (µg/m3)-1. You calculated the proposed CSF by applying a factor of 0.59 to the CSF of 1.4 per mg/kg/d developed by OEHHA. You state that your proposed CSF was developed using the U.S. EPA recommended

cross-species scaling factor of (BW3/4) and thus used a more current cross-species scaling factor for the study administered dose than OEHHA. However, the cross-species scaling factor (BW3/4) should be used to estimate the human equivalent dose (HED) from the animal data, and should not be used to adjust an already developed CSF. For this reason, the method used to develop the proposed oral CSF for NNN is not considered appropriate.

NNK *Cancer slope factor*: You proposed an oral CSF for NNK of 19 per mg/kg/d. You use this oral CSF in the QRA to develop an IUR of 5.2E-03 (µg/m3)-1. You calculated the proposed oral CSF using the BMDL10 calculated by Naufal et al. (2009) for lung tumor data published in the NNK oral exposure study by Rivenson et al. (1988). However, the evaluation by Naufal et al. (2009) indicates that NNK oral exposures resulted in increased tumors in the lung, pancreas, liver and nasal cavity. The study by Riverson et al., 1988 was also used by OEHHA to develop the CSF for NNK of 49 mg/kg/day; this value considered the increased tumor incidence across all tissues (i.e., lung, pancreas, liver, and nasal cavity). You needed to provide data or scientific evidence to demonstrate that the proposed CSF for NNK of 19 per mg/kg/d is more appropriate to estimate the upper-bound excess lifetime cancer risk for NNK exposure than the NNK CSF of 49 mg/kg/day (OEHHA 2001).

When deriving cancer potency factors, you needed to provide more detailed information about the rationale for the calculations of IURs, including all details on route-to-route extrapolations, dose response modelling, and statistical frameworks.

Risk Characterization
As discussed above, several issues were identified with the data inputs used for the risk characterization (e.g., HPHCs considered in the evaluation and toxicity values). For these reasons, the data, information and conclusions provided in the risk characterization were not considered adequately representative of the potential differences in non-cancer hazard and cancer risk between the new and predicate products.

PRA
You provided a probabilistic risk assessment (PRA) for the same HPHCs included in the QRA, and therefore, all the limitations of the QRA also apply to the PRA. In addition, although the assumed minimum, maximum and mean values for the distributions are provided, no justifications for the selected distributions are supplied, and the values selected for the parameters have several limitations that may restrict the applicability of the PRA, including:

a. *Cigarettes per day (CpD):* For the CpD, you used a BetaPERT distribution with a range of 0.03-100 CpD, and an average of 15.98 CpD. You state that, "*every day smokers smoked between 0 and 100 cigarettes per day, with an average value of 15.98 cigarettes per day*", citing the MMWR report from CDC (2014); this report seems to be incorrectly referenced in the text as CDC (2015). The report by CDC shows that among adult daily smokers, 40.3% smoked 10-19 CpD; 29.3% smoked 20-29 CpD; 23.3% smoked 1-9 CpD; and, 7.1% smoked ≥30 CpD. This data does not support the CpD range, and minimum of 0.03 you used in the PRA for "every day smokers". In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

b. *Exposure duration (ED):* For the exposure duration, you indicate using a BetaPERT distribution with a range from 6 months to 73 years, an average ED of 20.3 years. You state that, "*application of NHANES questionnaire data suggest that the duration of smoking ranged from 7 to 73 years, with a mean duration of 20.3 years*." These data indicate a minimum ED of 7 years, and do not support the minimum ED of 6 months used in your PRA. In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

c. *Daily inhalation rate (DIR):* For the DIR, you used a BetaPERT distribution with a range of 6.24 m^3/day to 23.26 m^3/day, and average of 13.51 m^3/day, references the US EPA Exposure Factors Handbook (USEPA 2011), table 6.4. The USEPA 2011 Exposure Factors Handbook provides inhalation rates for females, males, and combined (males and females) for different age groups, and could be used to obtain the best distribution fit on the data. You did not provide a rationale for using a BetaPERT distribution for the inhalation rate. Also, you did not provide a scientific rationale and evidence for how the use of the selected inhalation rates are appropriate for tobacco use exposure scenario.

You needed to provide evidence that the HPHCs considered in the PRA are representative of the relative composite risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, the PRA needed to include all measured HPHCs from the new and predicate products.

In conclusion, you needed to provide sufficient data and a detailed description of the results and analysis of the QRA/PRA to demonstrate that user exposure to the new product will not lead to increased toxicity or overall health risk when compared to the predicate product. For the PRA, you needed to provide a complete description of the design of the assessment or simulations such that it informs the comparison of health risks between the new and predicate products. If distributions are to be used in a PRA, you needed to provide select parameters that could provide insight into such a comparison of health risks. For example, distributions around parameters that differ between the product are more informative than distributions around population variables which should be the same between products. Finally, you needed to provide sufficient scientific evidence and a rationale to demonstrate that increase in formaldehyde levels in the new product compared to the predicate product does not cause the new product to raise different questions of public health.

6.3. DEFICIENCIES FOR SE0006211

A NSE order letter for SE0006211 should cite the following deficiency:

1. Your SE Report indicates a statistically significant increase in formaldehyde level in the new product compared to the predicate product. Formaldehyde is a carcinogen and a respiratory toxicant. The ingredient (b) (4), increased in the new product as compared to the predicate product, can produce formaldehyde upon pyrolysis. You provided an individual constituent and composite quantitative risk assessment (QRA) and a probabilistic risk assessment (PRA) as supporting evidence that HPHC changes between the new and predicate product does not cause the new product to raise different questions of public

health. While a QRA/PRA is not required for an SE Report, it can inform the substantial equivalence determination. However, the submitted QRA/PRA, in its present form, is insufficient to support the position that the increase in formaldehyde does not cause the new product to raise different questions of public health. Several issues were identified with the QRA/PRA approach you presented. Specifically, these include:

QRA

Hazard Identification:

A more comprehensive QRA is required to effectively compare the risks of the new product relative to the predicate product. The QRA did not include acetaldehyde, although there are increases in smoke yields of this HPHC in the new product relative to the predicate product. This selective use of HPHCs in the QRA calculations may introduce bias in the assessment of cancer and noncancer effects associated with exposure to the new and predicate products. In the context of evaluating differences between the new and predicate products in this SE Report, the Hazard identification section of the QRA should consider all the HPHCs that can inform whether the differences in product characteristics between the new and predicate products may cause the new product to raise different questions of public health. You needed to provide evidence that the HPHCs measured and considered in the QRA are representative of the relative cumulative risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, all measured HPHCs should be included in the QRA.

Hazard Characterization

You used toxicity values developed by CalEPA for acetaldehyde and formaldehyde, and values developed by Texas Commission for Environmental Quality (TCEQ) for acrolein and 1,3-butadiene. However, toxicity values for these compounds have also been developed by the U.S.EPA Integrated Risk Information System (EPA IRIS). Specifically, EPA IRIS reference concentrations (RfCs) have been published for acetaldehyde, acrolein and 1,3-butadiene; IURs were developed by EPA IRIS for acetaldehyde, 1,3-butadiene and formaldehyde. The toxicity values used may have a significant impact on the result of the risk assessment. In general, the EPA IRIS toxicity values are developed using the best available science, are transparent about the data and methodologies used, and undergo a rigorous peer review process. You needed to provide information and a rationale demonstrating why the CalEPA and TCEQ toxicity values are more appropriate than the toxicity values developed by EPA IRIS, for the evaluation of noncancer hazard and cancer risks associated with inhalation exposures to these HPHCs.

NNN and NNK: For NNN and NNK, you developed IURs using route-to-route extrapolation from their respective oral cancer slope factors (CSF). You assert that “absorption, metabolism, and distribution following oral and inhalation routes are equivalent.” However, you did not provide evidence to substantiate this claim. You needed to provide information relevant to the toxicokinetics and toxicodynamics for NNN and NNK via the oral and inhalation routes, to demonstrate that the methods and assumptions used for the route-to-route extrapolations are appropriate. In addition, the following issues were identified with the CSFs you proposed for NNN and NNK:

NNN *Cancer slope factor:* You proposed an oral CSF of 0.83 per mg/kg/d for NNN. You use this oral CSF in the QRA to develop an IUR of 2.4E-04 (µg/m3)-1. You calculated the proposed CSF by applying a factor of 0.59 to the CSF of 1.4 per mg/kg/d developed by OEHHA. You state that your proposed CSF was developed using the U.S. EPA recommended cross-species scaling factor of (BW3/4) and thus used a more current cross-species scaling factor for the study administered dose than OEHHA. However, the cross-species scaling factor (BW3/4) should be used to estimate the human equivalent dose (HED) from the animal data, and should not be used to adjust an already developed CSF. For this reason, the method used to develop the proposed oral CSF for NNN is not considered appropriate.

NNK *Cancer slope factor*: You proposed an oral CSF for NNK of 19 per mg/kg/d. You use this oral CSF in the QRA to develop an IUR of 5.2E-03 (µg/m3)-1. You calculated the proposed oral CSF using the BMDL10 calculated by Naufal et al. (2009) for lung tumor data published in the NNK oral exposure study by Rivenson et al. (1988). However, the evaluation by Naufal et al. (2009) indicates that NNK oral exposures resulted in increased tumors in the lung, pancreas, liver and nasal cavity. The study by Riverson et al., 1988 was also used by OEHHA to develop the CSF for NNK of 49 mg/kg/day; this value considered the increased tumor incidence across all tissues (i.e., lung, pancreas, liver, and nasal cavity). You needed to provide data or scientific evidence to demonstrate that the proposed CSF for NNK of 19 per mg/kg/d is more appropriate to estimate the upper-bound excess lifetime cancer risk for NNK exposure than the NNK CSF of 49 mg/kg/day (OEHHA 2001).

When deriving cancer potency factors, you needed to provide more detailed information about the rationale for the calculations of IURs, including all details on route-to-route extrapolations, dose response modelling, and statistical frameworks.

Risk Characterization
As discussed above, several issues were identified with the data inputs used for the risk characterization (e.g., HPHCs considered in the evaluation and toxicity values). For these reasons, the data, information and conclusions provided in the risk characterization were not considered adequately representative of the potential differences in non-cancer hazard and cancer risk between the new and predicate products.

PRA
You provided a probabilistic risk assessment (PRA) for the same HPHCs included in the QRA, and therefore, all the limitations of the QRA also apply to the PRA. In addition, although the assumed minimum, maximum and mean values for the distributions are provided, no justifications for the selected distributions are supplied, and the values selected for the parameters have several limitations that may restrict the applicability of the PRA, including:

a. *Cigarettes per day (CpD):* For the CpD, you used a BetaPERT distribution with a range of 0.03-100 CpD, and an average of 15.98 CpD. You state that, "*every day smokers smoked between 0 and 100 cigarettes per day, with an average value of 15.98 cigarettes per day*", citing the MMWR report from CDC (2014); this report seems to be incorrectly referenced in the text as CDC (2015). The report by CDC shows that among adult daily smokers, 40.3% smoked 10-19 CpD; 29.3% smoked 20-29 CpD; 23.3% smoked 1-9 CpD; and, 7.1% smoked ≥30 CpD. This data does not support the CpD range, and minimum of 0.03 you used in the PRA for "every day smokers". In

addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

b. *Exposure duration (ED):* For the exposure duration, you indicate using a BetaPERT distribution with a range from 6 months to 73 years, an average ED of 20.3 years. You state that, "*application of NHANES questionnaire data suggest that the duration of smoking ranged from 7 to 73 years, with a mean duration of 20.3 years*." These data indicate a minimum ED of 7 years, and do not support the minimum ED of 6 months used in your PRA. In addition, you did not provide information and a justification for the use of a BetaPERT distribution for the ED. Additional information is needed.

c. *Daily inhalation rate (DIR):* For the DIR, you used a BetaPERT distribution with a range of 6.24 m^3/day to 23.26 m^3/day, and average of 13.51 m^3/day, references the US EPA Exposure Factors Handbook (USEPA 2011), table 6.4. The USEPA 2011 Exposure Factors Handbook provides inhalation rates for females, males, and combined (males and females) for different age groups, and could be used to obtain the best distribution fit on the data. You did not provide a rationale for using a BetaPERT distribution for the inhalation rate. Also, you did not provide a scientific rationale and evidence for how the use of the selected inhalation rates are appropriate for tobacco use exposure scenario.

You needed to provide evidence that the HPHCs considered in the PRA are representative of the relative composite risk of the new and predicate products, including non-cancer hazard and cancer risk. For a better comparison of the composite cancer risks and non-cancer hazards of the new and predicate products, the PRA needed to include all measured HPHCs from the new and predicate products.

In conclusion, you needed to provide sufficient data and a detailed description of the results and analysis of the QRA/PRA to demonstrate that user exposure to the new product will not lead to increased toxicity or overall health risk when compared to the predicate product. For the PRA, you needed to provide a complete description of the design of the assessment or simulations such that it informs the comparison of health risks between the new and predicate products. If distributions are to be used in a PRA, you needed to provide select parameters that could provide insight into such a comparison of health risks. For example, distributions around parameters that differ between the product are more informative than distributions around population variables which should be the same between products. Finally, you needed to provide sufficient scientific evidence and a rationale to demonstrate that increase in formaldehyde levels in the new product compared to the predicate product does not cause the new product to raise different questions of public health.