FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review:

SE0006213 and SE0006214

SE0006213: Kool Blue Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	29%
Characterizing Flavor	Menthol
SE0006214: Kool Box	
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	20%
Characterizing Flavor	Menthol
Common Attributes of SE Reports	
Applicant	ITG Brands, LLC
Report Type	Provisional
Product Category	Cigarettes
Product Sub-Category	Combusted Filtered
Recommendation	
Issue Substantially Equivalent (SE) orders.	

Technical Project Lead (TPL):

Jeannie H. Jeong-im -S
2018.10.16 11:44:06 -04'00'

Jeannie Jeong-Im, Ph.D.
Chemistry Branch Chief
Division of Product Science

Signatory Decision:

☒ Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

Digitally signed by Matthew R. Holman -S
Date: 2018.10.16 11:56:01 -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:

SE0006213: Kool Blue Box	
Product Name	Kool Milds King Box
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	29%
Characterizing Flavor	Menthol
SE0006214: Kool Box	
Product Name	Kool Filter Kings Box
Package Type	Box
Package Quantity	20 cigarettes
Length	83 mm
Diameter	7.79 mm
Ventilation	10%
Characterizing Flavor	Menthol

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

1.2. REGULATORY ACTIVITY RELATED TO THIS REVIEW

FDA received one SE Report on March 22, 2011 from R.J. Reynolds Tobacco Company (RJRT). On March 21, 2013, FDA received a request for a 90-day extension (SE0007894) in anticipation of FDA issuing an Advice/Information Request letter (A/I) letter.[1] FDA issued an A/I letter and Acknowledgement letter on March 25, 2013. On April 11, 2013, FDA received an amendment (SE0008212) to address the timeline for supplementing provisional SE Reports. FDA issued an Extension Response letter on April 17, 2013, stating that once the applicant receives a notification letter informing them of the start of scientific review, any amendments received by FDA after the start date may not be reviewed. FDA issued a Public Health Impact (PHI) A/I letter on May 10, 2013. On June 7, 2013, FDA received the applicant's response to the PHI A/I letter (SE0008897 for SE0006213 and SE0008903 for SE0006214). On July 1, 2013, a PHI review was completed. A detailed review of the product characteristics prompted FDA to reassign the STNs from Tier 1 to Tier 2. On May 15, 2015, FDA received an amendment to the original SE Report for SE0006214 (SE0011845). On June 11, 2015, FDA received an amendment

[1] FDA issued A/I letters for 58 of the 227 total SE Reports submitted by RJRT on March 14, 2013. On March 19, 2013, FDA conducted a telecon to confirm that RAI Services Company would receive the additional 169 identical A/I letters, to include SE0006213 and SE0006214.

to the original SE Report for SE0006213 (SE0011976). On July 1, 2015, FDA received a request to transfer ownership of SE0006213 and SE0006214 to ITG Brands, LLC (TC0001328). However, FDA issued a Notification letter inadvertently to RJRT on October 13, 2015 to inform the company that the scientific review of these reports will commence in 45 days from issuance of the letter and the applicant could amend the reports before the review begins. In addition, on October 20, 2015, FDA received an amendment from RAI Services, on behalf of RJRT (SE0012511) where it was noted that RJRT will not submit any amendments for these reports because they are not the applicant of record. To remedy the situation, FDA issued a new Notification letter to ITG Brands, LLC on October 23, 2015. On December 3, 2015, FDA received the applicant's response to the October 23, 2015 Notification letter (SE0012703 for SE0006213 and SE0012706 for SE0006214). On December 21, 2015, FDA received an amendment from the applicant in response to an OCE email dated December 16, 2015 (SE0012775) to clarify predicate product name discrepancies. On December 21, 2015, FDA received an amendment to the original SE Report for SE0006213 (SE0012777). FDA issued an A/I letter on September 22, 2017. On November 17, 2017, FDA received the responses to the A/I letter (SE0014404). FDA issued a Preliminary Finding (PFind) letter on February 12, 2018. On February 14, 2018, FDA received a PFind Extension Request (SE0014526). On February 22, 2018, FDA emailed ITGB asking them to submit an official amended PFind Extension Request. On February 23, 2018, FDA received an Amended PFind Extension Request (SE0014551). FDA issued a PFind Extension Request Granted letter on February 27, 2018. On March 1, 2018, FDA received an unsolicited amendment (SE0014565) which contained clarification questions from the applicant in order for them to respond to the PFind letter. On March 15, 2018, FDA provided responses to the clarification questions. On April 17, 2018, FDA received an additional PFind Extension Request (SE0014629) due to the applicant sustaining weather-related damage to their testing facilities. FDA issued a PFind Extension Request Granted letter on April 30, 2018. On June 11, 2018, FDA received the response to the PFind letter (SE0014760).

Product Name	SE Report	Amendments
Kool Blue Box	SE0006213	SE0007894 SE0008212 SE0008897 SE0011976 SE0012511 SE0012703 SE0012775 SE0012777 SE0014404 SE0014526 SE0014551 SE0014565 SE0014629 SE0014760

Kool Box	SE0006214	SE0007894 SE0008212 SE0008903 SE0011845 SE0012511 SE0012706 SE0012775 SE0014404 SE0014526 SE0014551 SE0014565 SE0014629 SE0014760

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 Megan Nguyen on October 16, 2018. The reviews concluded that the SE Reports are administratively incomplete due to lack of first commercial market (FCM) date. FCM date is considered an administrative request and is not necessary to complete a scientific evaluation. Since FCM is not required to initiate scientific evaluation, lack of this information does not preclude scientific review.

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 January 6, 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 Tricia Johnson on April 4, 2016, Delshanee Kotandeniya on January 26, 2018, and Jikun Liu on July 26, 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:

SE0006213

- 2% – 7% increase in (b) (4)(b) (4)(b) (4)(b) (4) types
- 33% increase in (b) (4)(b) (4)
- 33% increase in (b) (4)(b) (4)
- 33% increase in (b) (4)(b) (4)(b) (4)(b) (4)(b) (4)
- 5% and 1% increase in menthol smoke yields under ISO and CI smoking regimen, respectively
- 33% increase in (b) (4)(b) (4)(b) (4)(b) (4)(b) (4)
- 33% and 30% increase in (b) (4)(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)
- 9% increase in mainstream smoke NNK yield under ISO smoking regimen

SE0006214

- 5% – 10% increase in (b) (4)(b) (4)(b) (4)(b) (4) types
- 37% increase in (b) (4)(b) (4)
- 19% increase in (b) (4)(b) (4)
- 8% and 5% decrease in menthol smoke yields under ISO and CI smoking regimen, respectively
- 10% and 17% increase in mainstream smoke 4-aminobiphenyl and NNN, respectively, under CI smoking regimen

The differences in characteristics identified above may influence HPHC yields. To address the HPHC concerns that may arise from these above differences (e.g., tobacco blend, ingredients other than tobacco), the applicant provided HPHC data from a surrogate tobacco product as the predicate product was no longer available for HPHC testing. It was determined that the surrogate tobacco product was sufficiently characterized to extrapolate the product composition to the predicate product. TOST[2] analysis of the HPHC data indicates that, under ISO regimen,[3] NNK level of the new product is not within analytical variability to that of the surrogate products in SE0006213. Under CI regimen,[4] smoke yields of 4-aminobiphenyl and NNN for the new and respective surrogate predicate products are not within analytical variability in SE0006214. However, the increase in 4-aminobiphenyl is minimal (0.3 ng/cig) and the increase does not cause the new product to raise different questions of public health. The increase in NNN was referred to toxicology for further evaluation. For SE0006213 and SE0006214, there was a 19% to 33% increase in (b) (4). The applicant provided menthol smoke yields.

[2] Two One-Sided T-test (TOST) is a statistical tool that calculates important analytical differences (IADs) using the Horwitz-Thompson equation.

[3] This is a non-intense smoking regimen. Parameters used to smoke tobacco products typically include a 35-mL puff volume, 60s puff interval, 2s puff duration, and no blocking of the filter ventilation holes.

[4] This is an intense smoking regimen. Parameters used to smoke tobacco products typically include a 55 mL puff volume, 30s puff interval, 2s puff duration, and 100% blocking of the filter ventilation holes.

TOST analysis of the menthol smoke yields indicates that they are within the analytical variability and therefore, the (b) (4) [redacted] in the tobacco filler does not cause the new products to raise different questions of public health. Therefore, the differences in characteristics between the new and corresponding predicate tobacco products do not cause the new tobacco products to raise different questions of public health from a chemistry perspective.

4.2. ENGINEERING

Engineering reviews were completed by Ouided Rouabhi on March 28, 2016, by Rashele Moore on January 29, 2018, and by Drew Katherine on July 30, 2018.

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

SE0006213

- 48% decrease in cigarette paper band diffusion
- 11% decrease in tobacco cut size

SE0006214

- 14% decrease in draw resistance
- 48% decrease in cigarette paper band diffusion
- 6% decrease in filter total denier
- 17% decrease in filter denier per filament
- 6% decrease in filter density
- 100% increase in filter ventilation
- 11% decrease in tobacco cut size

A decrease in tobacco cut size per inch produces a larger cut width of tobacco which may lead to a lower nicotine release rate. Additionally, in SE0006214, the filter ventilation is increased, which is expected to decrease the deliveries of HPHCs and smoke constituent yields. Therefore, the differences in tobacco cut size for both SE Reports and filter ventilation in SE0006214 do not cause the new products to raise different questions of public health from an engineering perspective. A decrease in band diffusion may increase smoke constituent yields. A decrease in cigarette draw resistance may result in differences in the difficulty of pulling air through the tobacco rod and, in turn, affect smoke constituent yields. A decrease in filter total denier, filter denier per filament, and filter density may affect filter efficiency and, in turn, smoke constituent yields. However, based on the smoke constituent data provided by the applicant, tar, nicotine, and carbon monoxide values decrease from the surrogate predicate product to the respective new product. Therefore, the decrease in band diffusion, draw resistance, filter total denier, filter denier per filament, and filter density in SE0006213 and SE0006214 does not cause the new products to raise different questions of public health from an engineering perspective. Therefore, the differences in characteristics between the new and corresponding predicate 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 Prince Awuah on June 7, 2017, January 25, 2018, and August 21, 2018.

The final toxicology review concludes that the new tobacco products have different characteristics related to product toxicology 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 deficiencies that have *not* been adequately resolved:

1. Both of your SE Reports provide updated HPHC data containing number of replicates and standard deviations. However, two carcinogenic HPHCs were increased in the mainstream smoke generated from the new products compared to the corresponding remanufactured predicate products:

   SE0006213
   - NNK (↑9% under ISO)

   SE0006214
   - NNN (↑17% under CI)

   Your updated tobacco blend composition information indicates that there is an increase in (b) (4)(b) (4) in the new products of SE0006213 (33%) and SE0006214 (37%), compared to the corresponding predicate products. Your data also indicates that there is an increase in (b) (4) in the new product of SE0006214 (10%). These changes are potentially related to the above HPHC increases.

   You submitted quantitative risk assessment (QRA) results to justify that the increase of these HPHCs do not raise different questions of public health. However, your submitted QRA and probabilistic risk assessment (PRA) have limitations that preclude FDA to determine whether these increases in HPHCs do not raise different questions of public health from a toxicological perspective. You need to provide a rationale or scientific evidence to explain why the increase of NNN and NNK in the new products compared to their corresponding predicate products do not cause the new products to raise different questions of public health.

2. Both of your SE Reports include a voluntarily submitted QRA and PRA as evidence to support your assertion that increases in HPHC levels in the new products as a result of tobacco blend and tobacco ingredient changes do not cause the new products to raise different questions of public health. While a QRA and a PRA are not required for a substantial equivalence evaluation, such analyses can inform the review process, if adequately described and supported. However, the submitted QRAs and PRAs are missing key information that is necessary for them to be useful in determining whether the product changes and HPHC increases cause the new products to raise different questions of public health. For FDA to review any risk assessment, provide a detailed account of the QRAs and PRAs completed in line with recommendations from the National Academy of Sciences (NRC, 2009). The PRAs you provided were for the same

HPHCs included in the QRAs, and therefore, all the limitations of the QRAs discussed below also apply to the PRAs. Provide the following information necessary to evaluate the submitted QRAs and PRAs:

a. In the 'Dose-response Assessment' section, you state that the following equation was used for the route-to-route extrapolation:

(b) (4)(b) (4)(b) (4)
(b) (4)

(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)
(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)(b) (4)
(b) (4)(b) (4)(b) (4)
(b) (4)(b) (4)(b) (4)
(b) (4)(b) (4)(b) (4)(b) (4)

You provided inhalation unit risk (IUR) values. However, you did not provide specific input data, or discuss any specific assumptions for each HPHC in extrapolating from an oral route of exposure to an inhalation route. You did not specifically discuss this extrapolation approach for any particular HPHC. In addition, as you stated, the route-to-route extrapolation is not equivalent, but you did not further adjust the extrapolated values to take into consideration the increased "*sensitivity of the respiratory tract"* or state for which HPHCs this applies.

You need to further explain the specific conversion from the oral to inhalation route on a case-by-case basis. For example, route-to-route extrapolation methods need to account for the relationship between physicochemical properties, the absorption and distribution of toxicants, the significance of portal-of-entry effects, and the potential differences in metabolic pathways associated with inhalation exposures versus oral (e.g. ingestion) exposures. Given these potential considerations, an assumption of 100% transferability may not reflect human risk.

b. Provide detailed selection criteria for the selection of reference values and scientific evidence for deviating from established reference values. Include additional evidence or rationale for selected reference values, given the availability of multiple reference values for a specific constituent. Any rationale should include scientific evidence for deviating in methodology from the National Research Council and the Guidelines for Carcinogen Risk Assessment.

c. Provide evidence that the reference values used in the calculation of the hazard quotient (HQ) or incremental lifetime cancer risk (ILCR), and used in both the QRAs and PRAs, are appropriate for the toxicological endpoints associated with the use of the new and predicate products and the expected user populations.

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 (i.e., Subject and Reman Predicate/Predicate).*" 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 specific evidence or rationale for the inclusion of body weight (BW) and daily inhalation rate in your estimation of exposure concentrations, including how the inclusion of these variables are appropriate for tobacco product-specific exposures as well as the population expected to use the new and predicate products. If you wish to use your own methodologies and include different variables such as BW, you need to clearly state how your methodologies and included variables are appropriate to cigarette smoking exposure and the selected user populations, and discuss the associated uncertainties for each variable, as well as their impact on the overall risk assessment uncertainty.

f. Provide clarification for any differences in exposure lifetime values and include scientific evidence and rationale that the expected exposure lifetime value is appropriate for the specific products and user populations.

g. Provide additional information on how the cumulative HQ and cumulative ILCR values were calculated, including 1) justification for the smoke HPHCs included, and 2) how to interpret the results of the cumulative ILCR and HQ (HI) based on distribution means resulting from the PRAs. If there is any HPHC that is significantly different in an analytically meaningful way in the new products compared to the corresponding Reman predicate products but was not included in the calculation of cumulative HQ/cumulative ILCR, provide an explanation as to how the omission of any HPHC can impact the results of a QRA or PRA.

h. Provide a complete description of each PRA design or simulations, such that it informs the comparison of health risks between the new and predicate products. For example, although the assumed minimum, maximum and “likeliest” values for the distributions are provided, no justifications for the use of Beta PERT distributions (used for Cigarettes per Day (CpD), Exposure Duration (ED), Averaging Time (AT)) or Gamma distribution (used for Daily Inhalation Rate (DIR)) are given. Provide scientific evidence that the parameter ranges and means are specific to the new and predicate products and the expected user populations. Consider the differences in potential hazards and risks to users of the new and predicate products, given upper percentile comparisons from the simulated distributions.

i. 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 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.

j. You provided PRA results to characterize uncertainty and variability associated with exposure-related parameters. However, the PRA does not include clear description

of several aspects of your computational methodology, input parameters, and interpretation of the assessment results. Importantly, the PRAs do not address uncertainties inherent to other QRA elements or include an assessment of each PRA's ability to discern a statistical difference in risk between tobacco products. Provide detailed characterization of uncertainty and variability of all other elements in the risk assessment process, such as 1) Uncertainty in the use of addition for estimating total hazard or risk from components of a mixture in which other interactions may occur or the available information indicates combinations other than additivity regarding dose effects and adverse health outcomes; 2) Uncertainty in representing the total adverse health risks of the new and predicate cigarette products with the selected HPHCs that are included in the QRAs/PRAs. For example, if you are only including a small number of HPHCs in a QRA or PRA, when you have provided a larger number of tested HPHCs, you need to discuss the rationale for this approach and associated uncertainties.

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. However, as TPL, I conclude that the above deficiencies should not be conveyed to the applicant because the 9% increase in NNK under ISO and 17% increase in NNN under CI for SE0006213 and SE0006214, respectively, although not within analytical variability, are noted in only one smoking regimen each. NNK under CI and NNN under ISO are within analytical variability. In addition, the submitted QRAs and PRAs are missing key information that would be necessary for them to be useful in determining whether the product changes and HPHC increases cause the new products to raise different questions of public health. In addition to TNCO, the applicant also provided the following HPHCs under ISO and CI smoking regimens: 1,3-butadiene, 1-aminonaphthalene, 2-aminomaphthalene, acetaldehyde, acrolein, acrylonitrile, ammonia, benzene, benzo[a]pyrene, crotonaldehyde, formaldehyde, isoprene, propylene oxide, and toluene. Along with TNCO, all these HPHC values are were within the acceptable analytical variability of the method. Therefore, based on the totality of evidence, this increase in a single HPHC per product identified in these SE Reports does not cause the new products to raise different questions of public health.

5. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act for these provisional SE Reports (SE0006213-SE0006214) is categorically excluded and, therefore, normally does not require the preparation of an environmental assessment (EA) or an environmental impact statement. FDA has considered whether there are extraordinary circumstances that would require the preparation of an EA and has determined that none exist.

6. CONCLUSION AND RECOMMENDATION

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

-

SE0006213

- 2% – 7% increase in [redacted] types
- 33% increase in [redacted]
- 33% increase in [redacted]
- 33% increase in [redacted]
- 5% and 1% increase in menthol smoke yields under ISO and CI smoking regimen, respectively
- 33% increase in [redacted]
- 33% and 30% increase in [redacted]
- 9% increase in mainstream smoke NNK yield under ISO smoking regimen
- 48% decrease in cigarette paper band diffusion
- 11% decrease in tobacco cut size

SE0006214

- 5% – 10% increase in [redacted] types
- 37% increase in [redacted]
- 19% increase in [redacted]
- 8% and 5% decrease in menthol smoke yields under ISO and CI smoking regimen, respectively
- 10% and 17% increase in mainstream smoke 4-aminobiphenyl and NNN, respectively, under CI smoking regimen
- 14% decrease in draw resistance
- 48% decrease in cigarette paper band diffusion
- 6% decrease in filter total denier
- 17% decrease in filter denier per filament
- 6% decrease in filter density
- 100% increase in filter ventilation
- 11% decrease in tobacco cut size

The applicant has demonstrated that these differences in characteristics do not cause the new tobacco products to raise different questions of public health. The new and predicate products have changes in the tobacco blend and some design parameters, but these do not raise different questions of public health based on TNCO and benzo[a]pyrene yields under ISO and CI smoking regimens. For SE0006214, there was a 10% increase in 4-aminobiphenyl for a 0.3 ng/cig increase. This increase is a minor increase and does not cause the new product to raise different questions of public health. There is a 9% increase in NNK under ISO for SE0006213 and 17% increase in NNN under CI for SE0006214 that are not within analytical variability based on the TOST analysis. However, these increases were only noted in one smoking regimen each and based on the totality of evidence including other HPHC decreases, this increase in a single HPHC per product identified in these SE Reports does not cause the new products to raise different questions of public health. Furthermore, filter ventilation changes result in a reduction in several HPHC yields. Additional information on the submitted QRA would have been helpful; however, additional information is not needed at this time on these SE Reports as there was only one minor increase in HPHCs in one smoking regimen. Therefore, the differences in characteristics between the new and predicate products do not cause the new products to raise different questions of public health.

The predicate tobacco products meet statutory requirements because it was determined 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. However, as explained above, I disagreed with the final toxicology review because after examining the totality of evidence, including other HPHC decreases, this increase in a single HPHC in a single smoking regimen per product identified in these SE Reports does not cause the new products to raise different questions of public health. Consequently, I recommend that SE order letters be issued.

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

SE order letters should be issued for the new tobacco products in SE0006213 and SE0006214, as identified on the cover page of this review.