U.S. FOOD & DRUG ADMINISTRATION

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

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Subject: R.J. Reynolds Tobacco Company SE Reports: SE0006198, SE0006199, SE0006211

Background

A TPL review was signed on May 3, 2018, by Matthew Walters. The review identifes the following statistically significant increases in formaldehyde yields from the new products compared to the corresponding predicate products:

- SE0006198: 10% (CI smoking regimen)
- SE0006199: 40% (CI smoking regimen)
- SE0006211: 20% (ISO smoking regimen)

The review recommends that NSE orders be issued for all of these SE Reports with the basis for the recommendation being a single deficiency regarding the formaldehyde yield increases. The applicant provided quantitative risk assessments (QRAs) and probabilistic risk assessments (PRAs) as supporting evidence that HPHC differences do not cause the new products to raise different questions of public health. The formaldehyde deficiency identifies issues with the QRAs and PRAs leading to these assessments not being adequate to demonstrate that the formaldehyde yield increases do not cause the new products to raise different questions of public health.

Discussion

I agree that the formaldehyde yield increases are significant and may cause the new products to raise different questions of public health. However, I found that all of the information in the administrative record, when evaluated in totality, is sufficient to conclude that the increases in formaldehyde yields do not cause the new products to raise different questions of public health.

The toxicology review by Ana DePina on June 20, 2017, concludes that the applicant needs to provide scientific evidence for why increases in formaldehyde yields do not cause the

new products to raise different questions of public health. In response, the applicant provided QRAs and PRAs in an effort to demonstrate that the totality of HPHC data shows that the new products do not raise different questions of public health from a toxicology perspective. The toxicology review by Kauser Ahmed on March 1, 2018, concludes that the QRAs and PRAs have shortcomings that prevent FDA from drawing conclusions about the toxicity of the new products relative to the corresponding predicate products. I agree with this conclusion. However, I do not believe QRAs or PRAs are needed to demonstrate that the increases in formaldehyde do not cause the new products to raise different questions of public health from a toxicology perspective. The chemistry review by Megan Mekoli on March 2, 2018, includes HPHC data results for all of the new and predicate products in Table 13. Data was reported for the following HPHCs under ISO and CI smoking regimens:

1. Nicotine
2. Tar
3. Carbon Monoxide (CO)
4. Acetaldehyde
5. Acrolein
6. Formaldehyde
7. Benzon(a)pyrene
8. Benzene
9. 1,3-Butadiene
10. Toluene
11. NNK
12. NNN
13. Nitrogen oxides (NOx)

The chemistry reviewer, toxicology reviewer, and TPL conclude that none of the HPHCs *except* formaldehyde had significant increases. They also conclude that formaldehyde yields were significantly increased under one of the smoking regimens but not the other. Based on the extensive list of HPHCs tested under both smoking regimens which did not reveal significant increases in HPHC yields other than formaldehyde, it does not seem likely that the formaldehyde yield increases under a single regimen are going to increase the toxicity of the new products. Furthermore, smoke yields for other volative organic compounds (VOCs) such as acrolein, acetaldehyde, and benzene did not increase in the new products compared the corresponding predicate products. Even without a QRA or PRA, it seems unlikely that the increase in formaldehyde yields would increase the toxicity of the new products in light of the twelve other HPHCs that did not increase. Therefore, taking all of the HPHC data together, I conclude that the increases in formaldehyde do not cause the new products to raise different questions of public health.

Conclusion

Based on the totality of the information within these SE Reports, in this case, the formaldehyde yield increases under a single smoking regimen do not cause the new products to raise different questions of public health. Therefore, OS will issue SE orders for these three new products.

Under 21 CFR 25.35(a), issuance of SE orders under section 910(a) of the FD&C Act for these provisional SE Reports 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.