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CONFIDENTIAL, NOT FOR PUBLIC DISCLOSURE

November 30, 2018

Hans Rosenfeldt, Ph.D.
Deputy Director, Division of Nonclinical Science
Deirdre Kittner, Ph.D., MPH
Deputy Director, Division of Population Health Science
Office of Science
Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: PARTIAL RESPONSE (DEFICIENCY 9) to AUGUST 10, 2018 ADVICE/INFORMATION REQUEST for PM0000427-PM0000432 and MR0000068-MR0000073

Dear Drs. Rosenfeldt and Kittner:

RAI Services Company ("RAIS")[1] hereby submits the following, on behalf of R.J. Reynolds Tobacco Company ("RJRT"), in response to the United States Food and Drug Administration's ("FDA") Center for Tobacco Products ("CTP") August 10, 2018, ADVICE/INFORMATION REQUEST letter regarding RAIS's submission of Premarket Tobacco Applications ("PMTAs") and Applications Seeking a Modified Risk Tobacco Product Order ("MRTP Applications"), submitted under Section 910(b) and Section 911(d) of the Food, Drug, and Cosmetic Act ("FDCA"), respectively, on March 30, 2017 for the following tobacco products:

- PM0000427/MR0000072, Camel Snus Robust
- PM0000428/MR0000070, Camel Snus Mellow

[1] RAI Services Company ("RAIS") bears primary responsibility for regulatory compliance for Reynolds American Inc.'s operating companies, including R.J. Reynolds Tobacco Company ("RJRT"), American Snuff Co., LLC ("ASC"), Santa Fe Natural Tobacco Company, Inc. ("SFNTC"), and R.J. Reynolds Vapor Company ("RJRV"). References to RAIS in this letter refer to itself and RJRT where applicable.

- PM0000429/MR0000069, Camel Snus Frost Large
- PM0000430/MR0000071, Camel Snus Mint
- PM0000431/MR0000073, Camel Snus Winterchill
- PM0000432/MR0000068, Camel Snus Frost

This response refers to Deficiency Nine (9) in the aforementioned ADVICE/INFORMATION REQUEST. Deficiencies not addressed in this submission will be covered in separate responses. In this response, we have repeated CTP's requests, verbatim and in bold italics, followed by RAIS's response.

Please note that the enclosed response may contain confidential commercial and non-public trade secret information belonging to RAIS, RJRT, or RJRT's vendors. All such confidential and trade secret information is exempt from public disclosure under § 301(j) and § 906(c) of the FDCA, 5 U.S.C. § 552(b)(4), 18 U.S.C. § 1905, and 21 C.F.R. § 20.61 and any similar or related laws and regulations. RAIS and RJRT respectfully request that FDA maintain the confidentiality of this information.

Should you have any questions or require any additional information, please contact me at your earliest convenience.

Respectfully submitted,

Michael W. Ogden, Ph.D.
Senior Vice President
Scientific & Regulatory Affairs
RAI Services Company

FDA-Listed Deficiencies and RAIS Response

9. ***For all your MRTPAs/PMTAs, you have not provided measured HPHC data from the specific test articles (products labeled "Camel Snus" and other tobacco products tested in your studies) used for the in vitro and in vivo assays submitted in this application. You need to provide HPHC information necessary to show that the toxicological comparisons made in your in vivo and in vitro studies can be extrapolated to the specific new products listed in your MRTPAs/PMTAs. The information provided indicates that Camel Snus test articles/product samples used for conducting the in vitro assays were received by the laboratory conducting these assays (Labstat International ULC) at various time points between 2008 and 2013; it is unclear when the test articles for the other products tested in these studies were obtained by the laboratory. For the in vivo experiments, the information provided indicates that the test articles ("Camel Snus native "tobacco blend containing no additives and aqueous extract of the Camel Snus tobacco blend) were received by the laboratory conducting the study (Battelle), on May 7, 2008. You provided analytical HPHC data obtained from Camel Snus products tested at various dates between 2013 and 2015. You also submitted studies (Section 7.1 of the MRTPAs/PMTAs) that report measured HPHC levels in the comparator smokeless tobacco and cigarette products. These HPHC data for the comparator tobacco products were obtained from commercial U.S. cigarettes and smokeless tobacco products in 2014 and 2015. However, you have not supplied HPHC data specific to the Camel Snus test articles used in the in vitro and in vivo assays submitted in this application, and did not provide HPHC data for the test articles of the comparator products used in the in vitro assay. These data are needed to perform a comprehensive toxicological evaluation, and to gain a better understanding of any differences in HPHC yields between the test articles used in the in vitro and in vivo assays, and the HPHC yields provided for the Camel Snus products and comparator products in this MRTPA/PMTA. Such information is needed to understand whether the test articles examined in your submitted studies are toxicologically comparable to the six Camel Snus products listed in your applications.***

   For each of your MRTPAs/PMTAs, provide HPHC data specific to the test articles used in the in vitro and in vivo assays, as appropriate. If these data are not available, provide pertinent information on any anticipated differences in HPHC levels between the test articles used in the bioassays and the HPHC yields provided for the specific Camel Snus products listed in your MRTPAs/PMTAs and comparator products, and how such differences may impact the interpretation of these in vitro and in vivo studies and extrapolation of the data to the evaluation of the six Camel Snus products in your MRTPAs/PMTAs.

RAIS RESPONSE TO DEFICIENCY 9

RAIS understands FDA's Deficiency 9 as a request to provide HPHC data for each of the MRTPAs/PMTAs, specific to the test articles used in the in vitro and in vivo assays, as appropriate. Or, if these data are not available for RJRT to provide pertinent information for any anticipated differences in HPHC levels between the test articles used in the bioassays and the HPHC yields provided for the specific Camel Snus products listed in the MRTPA/PMTA, as well as the comparator products. Furthermore, FDA requests that RAIS explain how such differences may impact the interpretation of these in vitro and in vivo studies.

RAIS would like to clarify that the chemistry study M195-GLP (*see* study report LSI 2014 113 submitted in the Camel Snus MRTPAs/PMTAs at the following location: \7_STUDANAL\7_1_CHEM\01_M195_CHEM\1_RPT\1_RPT\ M195-GLP_Final Study Report_April_23_14 – Rescanned.pdf) was conducted concurrently with the in vitro studies M194A-GLP and M194B-GLP and all three studies utilized the same samples of the six Camel Snus styles subject of the MRTPAs/PMTAs and two combustible cigarette comparators. As such, the HPHC data reported for the aforementioned chemistry study are specific to the test articles of the GLP in vitro studies. While supportive of the reduced toxicity of Camel Snus relative to combustible cigarettes, the remaining in vitro studies included in Section 7_2_INVITRO and sub-acute, sub-chronic, and chronic in vivo studies included in Section 7_3_INVIVO are legacy studies which were not designed or conducted for the purposes of these MRTPAs/PMTAs. Thus, HPHC analyses specific to the test articles of those studies were not contemplated nor was data collected.

However, RJRT has reviewed production specifications for all six Camel Snus styles which are the subject of the MRTPAs/PMTAs and determined that no tobacco blend differences exist over the years associated with the nonclinical studies submitted as part of the Camel Snus MRTPAs/PMTAs. Therefore, temporal variability in HPHCs are minimal (with expected variability due to agricultural, manufacturing, and analytical sources) and the HPHC data provided for the six Camel Snus styles in the MRTPAs/PMTAs can be extrapolated to the specific test articles of the legacy in vitro and in vivo studies. Evidence to this point is available through RJRT's internal monitoring program (*see* study report RDM JMR 2016, 235 submitted in the Camel Snus MRTPAs/PMTAs at the following location: \7_STUDANAL\7_1_CHEM\02_R019283_SMOKELESS\1_RPT\1_RPT\ RDM-JMR 2016 235 - Snus Chemistry Report.pdf) (b) (4)

In conclusion, HPHC data from the M195-GLP study represents the test articles in the M194A-GLP and M194B-GLP in vitro studies. Further, RJRT has confirmed, through specification review and analytical monitoring, Camel Snus product consistency over the time interval in which all in vitro and in vivo studies cited in MRTPAs/PMTAs were conducted. Thus, all HPHC data provided in the MRTPAs/PMTAs for the six Camel Snus styles can be extrapolated to the specific test articles for which the toxicological comparisons were made and all studies are representative of the six Camel Snus styles subject of these applications.