RAI Services Company

Michael W. Ogden, Ph.D.
Senior Vice President
Scientific & Regulatory Affairs
Winston-Salem, NC 27101
336-741-5787
Fax: 336-728-7675
ogdenm@rjrt.com

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October 17, 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 17) 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.

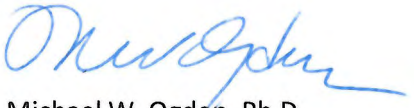
- PM0000429/MR0000069, Camel Snus Frost Large
- PM0000430/MR0000071, Camel Snus Mint
- PM0000431/MR0000073, Camel Snus Winterchill
- PM0000432/MR0000068, Camel Snus Frost

This response refers to Deficiency Seventeen (17) 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,



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FDA-Listed Deficiencies and RAIS Response

17. ***All of your MRTPAs/PMTAs provide an operational definition of AE relatedness in six RJRT-sponsored clinical studies (Section 7_4). You typically assessed AE relatedness on a four-point scale: not related, possibly related, probably related and definitely related. In addition, one study (08_CSD1101_STM) used a five-point scale, including the following descriptor: "unlikely related." These relatedness definitions employed concepts of:***

    - ***Temporality to the use of "study material" (01-HSD0702_QOL), "trial material" (03_CSD0901_SSSO), "test product" (07_CSD1010_SS), and "study product" (04_CSD0904_PMS; 06_CSD0914_SUL and 08_CSD1101_STM) or "concurrent treatment" (all six studies)***
    - ***Other plausible explanations including "concomitant medications" and "concurrent treatment" (all six studies)***
    - ***Definitely related events both followed a reasonable temporal sequence from material or product use, followed a known or hypothesized cause-effect relationship, and (if appropriate) satisfied a) positive results obtained in material or product sensitivity tests and b) toxic level of the material or product present in blood or other body fluids (five studies – excluded 08_CSD1101_STM)***

    Address the following issues:

    a. Clarify the meaning of the term "concurrent treatment" for each study using the term. How does "concurrent treatment" differ from "concomitant medications" and does it encompass dual or poly tobacco product use?

    b. For all of your RJRT-sponsored clinical studies, clarify if the AE data coding you submitted considers the collected biomarker results, or if coding was completed before product bench analyses and biomarker results were available.

RAIS RESPONSE TO DEFICIENCY 17

a. "Concurrent treatment" is defined as a non-medicinal treatment or a non-medicinal therapy a subject is taking during their participation in the clinical study, but this treatment/therapy is not one of the investigational products studied in the clinical study. "Concomitant medications" is defined as a drug or medication a subject is taking during their participation in the clinical study, but this drug/medication is not one of the investigational products studied in the clinical study.

   Dual or poly tobacco use is not considered a concurrent treatment. However, it is a factor that the Principle Investigator would have taken into account when making his determination of relationship to study product (i.e., other plausible explanations). For example, in the event that a subject had a thermal burn related to a combustible cigarette, this event would be recorded as an AE, but would not be related to the study product.

b. Biomarker results were not available until after the conclusion of the clinical phase of the study; consequently, AE data coding was performed without consideration of the biomarker results.