RAI Services Company

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CONFIDENTIAL, NOT FOR PUBLIC DISCLOSURE

October 18, 2018

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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 6) 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 Six (6) 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
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RAI Services Company

6. ***All of your MRTPAs/PMTAs list final Camel Snus product design specifications*** (b) (4) (b) (4) ***These ranges could result in a range of nicotine release rates and total nicotine released from the products. Provide scientific evidence that the ranges that correspond to the high and low rejection limits, and any other process controls, minimize the variability in the levels of nicotine released.***

   One way to potentially demonstrate that rejection limits for tobacco product parameters minimize the variability in levels of nicotine released may be through the measurement of nicotine release rates and total nicotine content from the products. The nicotine release rate and total nicotine release could be obtained through studies of nicotine content in artificial saliva (using in vitro dissolution experiments), which may potentially provide evidence of minimized variability. If you choose to provide nicotine release data, including the following would help FDA in its evaluation of the study:

   a. ***Description of the dissolution apparatus (apparatus type, media volume);***
   b. ***Description of the dissolution conditions (media, temperature, stir/flow rate, etc.);***
   c. ***Description of the dissolution media (pH, buffers, enzymes, buffer capacity, degassing, etc.);***
   d. ***Description and rationale for the sampling time points (should include 3 time points in initial release period and no more than 2 time points in the steady state portion of the release curve);***
   e. ***Description of sample size and disposition (how much is added to the vessel, was a sinker used, etc.);***
   f. ***Percentage nicotine released relative to a t∞ for each sample vs time plots for a representative sample of the products (t∞ is determined by increasing the flow rate for a period of time after steady state is reached);***
   g. ***Complete description of quantitative test protocols and method used;***
   h. ***Method validation status and validation reports and data for the nicotine analytical method;***
   i. ***Testing laboratory and their accreditation(s);***
   j. ***Length of time between date(s) of manufacture and date(s) of testing;***
   k. ***Number of replicates;***
   l. ***Standard deviation(s);***
   m. ***Complete data sets;***
   n. ***A summary of the results for all testing performed; and***
   o. ***Storage conditions prior to initiating testing.***

If you choose to use a different way to potentially demonstrate that rejection limits for tobacco product parameters minimize the variability in the levels of nicotine released, provide the following (to the extent applicable):

- ***p. Complete description of the test protocols (quantitative and qualitative) and method(s) used;***
- ***q. A scientific rationale explaining why this way is appropriate and adequate to potentially demonstrate how and why the rejection limits for tobacco product parameters minimize the variability in the levels of nicotine released in the new tobacco products;***
- ***r. Description of the apparatuses used such as apparatus type, and media volume;***
- ***s. Description of the test conditions such as media, temperature, stir/flow rate, etc.;***
- ***t. Description of the any media used such as pH, buffers, enzymes, buffer capacity, degassing, etc.;***
- ***u. Description and rationale for any sampling time points (should include 3 time points in initial release period and no more than 2 time points in the steady state portion of the release curve);***
- ***v. Description of sample size and disposition how much is used for each sample test-point and any manipulations that are performed with the sample prior to testing;***
- ***w. All formulas and calculations for how determining that the test data demonstrates that the rejection limits for tobacco product parameters minimize the variability in the levels of nicotine released this may include the information within item (f) above;***
- ***x. Method validation status and validation reports and data for the nicotine analytical method;***
- ***y. Testing laboratory and their accreditation(s), when applicable;***
- ***z. Length of time between date(s) of manufacture and date(s) of testing;***
- ***aa. Number of replicates;***
- ***bb. Standard deviation(s);***
- ***cc. Complete data sets;***
- ***dd. A summary of the results for all testing performed; and***
- ***ee. Storage conditions prior to initiating testing.***

RAIS GENERAL RESPONSE TO DEFICIENCY 6

RAIS understands FDA's request to be to demonstrate that (b) (4) (b) (4) . RAIS would

first like to reiterate (b) (4)

(b) (4)

[1] Fisher, M.T. et al. Sources of Technical Approaches for the Abatement of Tobacco Specific Nitrosamine Formation in Moist Smokeless Tobacco Products. *Food and Chemical Toxicology*. **2012**, 50, 942-948.
[2] Davis, D.L.; Nielson, M.T. Tobacco: Production, Chemistry and Technology. *Blackwell Science*. **1999**, 265-284.
[3] Shah, VP, Lesko, LJ, Fan, J, Fleisher, N, Handerson, J, Malinowski, H, Makary, M, Ouderkirk, L, Rey, S, Sathe, P, Singh, GJP, Tillman, L, Tsong, Y, and Williams RL. FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. *Dissolut. Technol*. November **1997**, 15-22.
[4] Suarez-Sharp, S, Delvadia, PR, Dorantes, A, Duan, J, Externbring, A, Gao, Z, Ghosh, T, Miksinski, SP, and Seo P. Regulatory Perspectives on Strength Dependent Dissolution Profiles and Biowaiver Approaches for Immediate Release (IR) Oral Tablets in new Drug Applications. The AAPS Journal. 18(3), **2016**, 578-588

(b) (4)

Because smokeless tobacco products like Camel Snus are designed to be discarded after use, and dissolution experiments are not designed to provide information about what portion of constituents remain in a product after being discarded, dissolution testing of tobacco products is not an indicator of in vivo assessment results, i.e., actual exposure. Also, product use behaviors for smokeless tobacco products vary greatly among adult tobacco consumers. The variable nature of product use behavior has been demonstrated to be the greatest driver in exposure to tobacco constituents, as discussed in the Camel Snus MRTPAs/PMTAs. As such, it is clear that dissolution testing for the oral smokeless tobacco products is not an appropriate or reliable indicator of nicotine exposure. Actual exposure data were provided previously within the MRTPAs/PMTAs for Camel Snus and a summary of those data is provided herein.

[5] Kramer, J, Steinmetz, R, and Stippler, E. "Dissolution Method Development with a View to Quality Control." Pharmaceutical Dissolution Testing. Edited by Jennifer Dressman, and Johannes Kramer. Taylor & Francis Group, LLC, 2005, 315-351.
[6] Marques, MRC, Loebenberg, R, and Almukainzi, M. Simulated Biological Fluids with Possible Applications in Dissolution Testing. *Dissolut Technol*. August **2011**, 15-28.
[7] Markl, D, and Zeitler, JA. A Review of Disintegration Mechanisms and Measurement Techniques. *Pharm Res*. **2017,** 34(5), 890-917.

Camel Snus use results in exposure to only a fraction of the nicotine present in the tobacco

Exposure to constituents present in a tobacco product is the result of multiple factors, including the manner of use (e.g., inhalation vs. placement of tobacco in the mouth), product use behaviors (e.g., cigarette puffing behavior or time smokeless tobacco held in mouth), the chemical composition of the smoke or tobacco product, and the route(s) of exposure. It is well understood that the amount of nicotine (or any other constituent) present in a tobacco product itself is not an accurate predictor of the quantity of nicotine (or any other constituent) that is transferred from the product and results in actual exposure.

RJRT clinical studies submitted in the Camel Snus MRTPAs/PMTAs show that Camel Snus use results in exposure to only a fraction of the nicotine present in the tobacco because Camel Snus pouches are not ingested during use. Camel Snus users typically place the pouch between their upper lip and gum, and discard the pouch after a period of use. RJRT-sponsored clinical studies of actual product use by natural adopters and by product switchers have included chemical analysis of compounds (including nicotine) present in Camel Snus pouches before and after use. The differences in those quantities (before/after) provide estimates of the amounts of nicotine depleted from the pouch during use, i.e., the "mouth-level" exposure (MLE) experienced when using Camel Snus. MLE is an estimate of maximum potential exposure to a particular constituent in the product. With respect to nicotine, the MLE data from RJRT-sponsored clinical studies show that Camel Snus users are exposed to only a fraction of the nicotine present initially in Camel Snus pouches (see Camel Snus MRTPAs/PMTAs, Section 2, Table 2.9.1-10, reproduced below in Table 1.)

Nicotine MLE was assessed in various studies submitted with the Camel Snus MRTPAs/PMTAs - CSD0804, CSD0901, CSD0904, CSD0905, CSD0914 and HSD0702. These studies demonstrated that mean nicotine quantities ranging from 20% to 39% were removed during actual Camel Snus product use, far less than half of the nicotine present in the Camel Snus pouches.

Table 1: Mouth-Level Exposure (MLE) Studies of External Nicotine Exposure for Exclusive Camel Snus Users and Dual Users* of Camel Snus and Cigarettes (Table 2.9.1-10 Camel Snus MRTPAs/PMTAs)				
Study	**Study Design**	**Product Use Condition**	**Nicotine MLE (mg/pouch)[a]**	**% Nicotine Removed from Pouch [b]**
CSD0804	Cross-sectional	Camel Snus	2.8 (1.7)	39.2 (23.0)
CSD0901	Switching	Camel Snus [c]	2.7 (1.2)	39.7
CSD0901	Switching	Dual Use [c]	2.7 (1.3)	39.3
CSD0904	Cross-sectional	Camel Snus (pre-clinic)	1.9 (1.6)	38.5 (30.9)
CSD0904	Cross-sectional	Dual Use (pre-clinic)	1.1 (1.7)	21.3 (33.7)
CSD0904	Cross-sectional	Camel Snus (in-clinic)	1.8 (1.6)	35.7 (31.7)
CSD0904	Cross-sectional	Dual Use (in-clinic)	1.0 (1.5)	20.0 (28.1)
CSD0905	Switching	Dual Use	1.6 (1.1)	22.2 (14.7)
CSD0914	Single Use	Camel Snus	2.3 (1.6)	31.7 (22.8)
HSD0702[d]	Switching	Dual Use [e]	1.8 (1.1)	32.4 (20.7)

* Concurrent use of Camel Snus and cigarettes
[a] Mean (standard deviation)
[b] Mean (standard deviation). When standard deviation is not shown, the mean value was calculated from means of mouth-level nicotine and nicotine remaining in used Camel Snus pouches.
[c] Day 5 use results
[d] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.
[e] 24-week use results

Thus, MLE data demonstrate that Camel Snus use results in exposure to only a fraction of the nicotine present in the tobacco, the variable nature of product use behavior is a principal driver of exposure to nicotine and that dissolution testing for the oral smokeless tobacco products, such as Camel snus, is not a reliable indicator of actual nicotine exposure.[6]

Biomarkers of exposure provide the most relevant information regarding exposure to nicotine among product users

Biomarkers of exposure refer generally to any chemical, or its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism.[8] Biomarkers may be the constituents themselves; metabolites of the constituents in urine, blood, breath, saliva, nails, or hair; or protein- or DNA-binding products (adducts) of the constituents or their metabolites.[9]

Biomarkers of exposure measure actual exposure to constituents of tobacco as opposed to chemical analyses of the tobacco products, which provide information about specific characteristics of a tobacco product, such as nicotine content, but cannot predict actual exposures in product users. As noted previously, exposure to constituents present in a tobacco product or tobacco smoke is the result of

[8] Institute of Medicine. 2012. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, D.C.
[9] Institute of Medicine. 2012. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, D.C. pg 81.

multiple factors, including the manner of use (e.g., inhalation vs. placement of tobacco in the mouth), product use behaviors (e.g., cigarette puffing behavior or time smokeless tobacco held in mouth), the chemical composition of the smoke or tobacco product, and the route(s) of exposure. A key advantage of human exposure biomarkers over measurements of either product composition or product yield assessed via machine smoking methods is that biomarkers provide a realistic and direct assessment of toxicant dose for an individual, and are considered reliable metrics of the levels of exposure that consumers actually experience when using tobacco products.[10,11] Biomarkers of exposure offer the advantage of integrating product differences and product use behaviors to measure an individual's constituent or toxicant exposure over hours, days, or weeks, depending on the specific compound's clearance rate in an individual user.[12,13]

RJRT's Camel Snus MRTPAs/PMTAs included data from eight RJRT-sponsored clinical studies of Camel Snus that investigated product use behaviors, biomarkers of exposure, and other health-related endpoints. RJRT's clinical studies of Camel Snus are based on various designs, including: (a) cross-sectional evaluation of natural adopters of Camel Snus, (b) randomized controlled trials of product switching (ambulatory and confined) and (c) a randomized trial of smokers with an intent to quit smoking, who were switched to either Camel Snus or a nicotine replacement therapy (NRT) product to assess smoking cessation rates. Many of these studies evaluated users' nicotine exposure from the Camel Snus products that are the subject of the MRTPAs/PMTAs. Study endpoints included nicotine biomarkers of exposure and nicotine pharmacokinetics measures. Biomarkers of nicotine exposure relevant to tobacco use were assessed in biological matrices such as blood and urine.

Use of different Camel Snus pouch sizes results in similar exposure to nicotine and TSNAs

Camel Snus is marketed in two pouch sizes, 0.6 g and 1 g. To examine whether differences in toxicant exposures may occur based on pouch size, data is presented from a range of internal and external clinical studies. These studies show that Camel Snus users are exposed to similar levels of nicotine, regardless of whether they use 0.6 g or 1 g Camel Snus pouch sizes (see MRTPAs/PMTAs Section 2.9.1.2.9).

[10] Hecht SS, Yuan JM, and Hatsukami D. Applying tobacco carcinogen and toxicant biomarkers in product regulation and cancer prevention. *Chem Res Toxicol*. **2010**, 23:1001-1008.
[11] Chang CM, Edwards SH, Arab A, Del Valle-Pinero A, Yang L, and Hatsukami DK. Biomarkers of tobacco exposure: summary of an FDA-sponsored public workshop. *Cancer Epidemiol. Biomarkers Prev*. **2006**, 26(3):1-12.
[12] Ashley DL, O'Connor RJ, Bernert JT, Watson CH, Polzin GM, Jain RB, Hammond D, Hatsukami DK, Giovino GA, Cummings KM, McNeill A, Shahab L, King B, Fong GT, Zhang L, Xia Y, Yan X, and McCraw JM. Effect of differing levels of tobacco-specific nitrosamines in cigarette smoke on the levels of biomarkers in smokers. *Cancer Epidemiol. Biomarkers Prev*. **2010**, 19:1389-1398.
[13] Gregg EO, Minet E, and McEwan M. Urinary biomarkers of smokers' exposure to tobacco smoke constituents in tobacco products assessment: a fit for purpose approach. *Biomarkers.* **2013**, 18(6):467-86.

Four RJRT-sponsored clinical studies of 0.4 g and 0.6 g Camel Snus styles (CSD0901, CSD0904, CSD0905 and HSD0702) and one external study of primarily 1.0 g Camel Snus styles by Hatsukami et al. 2016[14] evaluated nicotine exposure. To compare urinary biomarker results from the different studies in order to assess potential exposure differences due to Camel Snus pouch size, selected biomarker results from RJRT-sponsored studies were converted (see Camel Snus MRTPAs/PMTAs Section 7, RDM PC 2016 175-a) to the units reported by Hatsukami et al. 2016. Based on the biomarker endpoints reported in that study, total cotinine and total nicotine equivalents were transformed (as discussed in the Camel Snus MRTPAs/PMTAs Section 7).

Similar nicotine biomarker levels were observed for all Camel Snus pouch sizes (see Camel Snus MRTPAs/PMTAs Table 2.9.1-11, reproduced below in Table 2). No trends associated with Camel Snus pouch size were evident, with mean nicotine biomarker levels for users of 0.4 g and 1.0 g products falling largely within the range observed for users of 0.6 g products. The consistency of these biomarker results across various studies suggests that Camel Snus pouch size is not a principal driver of exposure to nicotine.

[14] Hatsukami DK, Severson H, Anderson A, Vogel RI, Jensen J, Broadbent B, Murphy SE, Carmella S, and Hecht SS. Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching. *Tob Control* **2016**, 25:267-274.

Table 2: Urinary Nicotine Biomarkers by Exclusive or Dual Camel Snus Use* (Table 2.9.1-11 Camel Snus MRTPAs/PMTAs)

Study	Study Design	Camel Snus Pouch Size (g)	Duration of Use (weeks)	Total Nicotine Equivalents (nmol/mL)			Total Cotinine (ng/mL)		
				Mean	SD	N	Mean	SD	N
Exclusive Camel Snus Use									
CSD0901	Switching	0.6	1	30.0	30.2	30	1974	2099	30
CSD0904[a]	Cross-sectional	0.6	24+	41.9	49.3	50	2417	2338	50
Hatsukami et al. 2016[b]	Switching	1.0	4	35.6	31.0	53	2152	2005	53
Dual Use									
HSD0702[c,d]	Switching	0.4	24	43.0	16.8	29	3054	1421	29
CSD0901	Switching	0.6	1	40.9	21.1	29	2564	1397	29
CSD0904[a]	Cross-sectional	0.6	24+	65.5	53.6	50	3866	2937	50
CSD0905	Switching	0.6	4	76.2	50.9	33	4065	2704	33
Hatsukami et al. 2016[b]	Switching	1.0	4	55.7	43.0	100	3079	2398	100

* Concurrent use of Camel Snus and cigarettes
[a] One subject in the Camel Snus group and one subject in the Dual Use group used 1.0 g pouch size products.
[b] Some participants who experienced adverse effects from use of 1.0 g pouch size products were provided 0.6 g pouch size products.
[c] Intent-to-treat subject group. Similar results were observed for the per-protocol subject group.
[d] Subject compliance with assigned study product was less than 100%, making estimates relevant to dual use.

Camel Snus use results in either similar or reduced exposure to nicotine compared with cigarette smoking

Exclusive Camel Snus use results in either similar or reduced exposure to nicotine when compared with exclusive cigarette smoking. Two RJRT-sponsored studies (CSD0901, CSD0904), as well as three studies in the published literature (Hatsukami et al. 2016, Kotlyar et al. 2011, Cobb et al. 2010), examined biomarkers of nicotine exposure in exclusive Camel Snus users (product switchers and natural product adopters) compared with exclusive cigarette smokers.[14,15,16] Studies of smokers who switched to Camel Snus uniformly show reductions in urinary total nicotine equivalents, plasma nicotine and plasma cotinine (see, e.g., CSD0901, Hatsukami et al. 2016, Kotlyar et al. 2011).

[15] Kotlyar M, Hertsgaard LA, Lindgren BR, Jensen JA, Carmella SG, Stepanov I, Murphy SE, Hecht SS, and Hatsukami DK. Effect of oral snus and medicinal nicotine in smokers on toxicant exposure and withdrawal symptoms: a feasibility study. Cancer Epidemiol. *Biomarkers Prev*. **2011**, 20(1):91-100.
[16] Cobb CO, Weaver MF, and Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tob Control* **2010**, 19(5):367-73.

An RJRT study of Camel Snus adopters (CSD0904) found equivalent levels of urinary total nicotine equivalents and blood cotinine in exclusive Camel Snus users compared to exclusive cigarette smokers, but reported lower levels of blood nicotine for Camel Snus users. There are no biomarker data suggesting that Camel Snus users are exposed to higher levels of nicotine than cigarette smokers. The biomarker data for exclusive Camel Snus users and exclusive cigarette smokers are summarized in the Camel Snus MRTPAs/PMTAs, Table 2.9.1-3, and reproduced below in Table 3.

Table 3: Biomarker Studies of Nicotine Exposure from Exclusive Camel Snus Use Compared to Exclusive Cigarette Use (Table 2.9.1-3 Camel Snus MRTPAs/PMTAs)

Study	Measurement Type	Sample Matrix	Study Design	Relative Nicotine Exposure [a]		
				Camel Snus < Cigarettes	Camel Snus ≈ Cigarettes	Camel Snus > Cigarettes
CSD0901	Total Nicotine Equivalents [b]	24-hr Urine	Switching (confinement)	X		
CSD0901	Nicotine	Plasma	Switching (confinement)	X		
CSD0901	Cotinine	Plasma	Switching (confinement)	X		
CSD0901	Total Nicotine Equivalents [b]	Feces	Switching (confinement)		X	
CSD0904	Total Nicotine Equivalents [b]	24-hr Urine	Cross-sectional (natural adopters)		X	
CSD0904	Nicotine	Blood	Cross-sectional (natural adopters)	X		
CSD0904	Cotinine	Blood	Cross-sectional (natural adopters)		X	
Cobb et al. 2010	Nicotine	Plasma	Single Use [c]	X		
Hatsukami et al. 2016	Total Nicotine Equivalents[d]	Urine	Switching (ambulatory)	X		
Hatsukami et al. 2016	Total Cotinine	Urine	Switching (ambulatory)	X		
Kotlyar et al. 2011	Cotinine	Urine	Switching (ambulatory)	X [e]		

[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette biomarker results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette biomarker results.
[b] Unconjugated nicotine and the 9 metabolites were converted to molar unconjugated nicotine equivalents and summed.
[c] Product used twice during a single clinical session
[d] The sum of total nicotine, total cotinine and total 3'hydroxycotinine
[e] Some dual use of cigarettes and Camel Snus occurred during the study. As reported, 9.1% of subjects smoked on average more than 3 cigarettes per day.

Smoking one cigarette results in significantly greater and more rapid nicotine exposure than when using one Camel Snus pouch

Smoking a cigarette results in significantly greater and more rapid nicotine exposure than when using a pouch of Camel Snus. It is accepted that nicotine has a prominent role in the abuse liability of tobacco

products[17] and that clinical pharmacokinetic measures of nicotine, along with other information, provide a means for evaluating the abuse liability of a tobacco product. FDA thus recommends that applicants submit human studies "to assess the abuse liability and potential for misuse of the product as compared to other tobacco products on the market".[18]

RJRT-sponsored pharmacokinetic studies of Camel Snus users and cigarette smokers show that smoking a single cigarette results in greater nicotine exposure over time (AUC), a greater peak plasma nicotine exposure (C_{max}) and a peak plasma exposure that occurs significantly more quickly (T_{max}) than with the use of a single Camel Snus pouch (see CSD0905, CSD0914, CSD1101).

The results of RJRT-sponsored studies of clinical pharmacokinetic measures of nicotine during Camel Snus use are summarized below in Table 4 and are consistent with other systemic exposure data regarding nicotine and its metabolites taken from each of the switching, single-use and cross sectional studies presented in this response (see Table 3). Although these pharmacokinetic data suggest that Camel Snus exhibits significantly reduced abuse liability compared to cigarettes, Camel Snus nicotine delivery is on par with or can exceed that of approved smoking cessation products.[16,19] Thus, Camel Snus is expected to benefit smokers who are concerned about the risks of smoking, but who find medicinal NRT products unacceptable and will continue to use some form of tobacco product. While the ultimate population impact of Camel Snus as an MRTP will depend on factors beyond abuse liability, an evaluation by Pinney Associates concluded that Camel Snus appears to fall in the general "midrange" for a viable harm reduction product.[19]

Additional discussion of the abuse liability of Camel Snus relative to cigarettes, including a more detailed discussion of the quantitative and qualitative data produced by studies conducted by RJRT and others, is found in the Camel Snus MRTPAs/PMTAs Section 2.9.2, Section 6.1.6 and Henningfield et al. 2017.

[17] U.S. Department of Health and Human Services. 2014. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
[18] Food and Drug Administration. 2012. Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products.
[19] Henningfield, JE, Fant, RV, and Kleykamp, BA. An Assessment of Camel Snus Abuse Liability. **2017**. Submitted previously in the Camel Snus MRTPAs/PMTAs, Section 7.

Table 4: Pharmacokinetic Studies of Nicotine from Exclusive Camel Snus Use Compared to Exclusive Cigarette Use

Study	Measurement Type	Sample Matrix	Study Design	Relative Nicotine Exposure[a,b]		
				Camel Snus < Cigarettes	Camel Snus ≈ Cigarettes	Camel Snus > Cigarettes
CSD0905	Nicotine C_{max}	Serum	Single Use	X		
CSD0905	Nicotine AUC_{0-90}	Serum	Single Use	X		
CSD0905	Nicotine T_{max}	Serum	Single Use			X
CSD0914	Nicotine C_{max}	Serum	Single Use	X		
CSD0914	Nicotine AUC_{0-180}	Serum	Single Use	X		
CSD0914	Nicotine T_{max}	Serum	Single Use			X
CSD1101	Nicotine C_{max}	Serum	Single Use	X		
CSD1101	Nicotine AUC_{0-180}	Serum	Single Use	X		
CSD1101	Nicotine T_{max}	Serum	Single Use			X

*Data are based upon exclusive single use of either Camel Snus or usual brand (UB) cigarette during a clinic visit.
[a] An "X" in either the "Camel Snus < Cigarettes" or "Camel Snus > Cigarettes" columns indicates a statistically significant difference between Camel Snus and cigarette pharmacokinetic results, with Camel Snus less than or greater than cigarettes, respectively. An "X" in the "Camel Snus ≈ Cigarettes" column indicates that no statistically significant difference was observed between Camel Snus and cigarette pharmacokinetic results.
[b] For T_{max} measurements, marks are indicative of relative time to reach T_{max} and do not indicate greater relative exposure.

Camel Snus use results in reduced exposure to nicotine compared with moist snuff

The primary objective of CSD0904 was to establish baseline values for tobacco constituent/toxicant exposure levels, tobacco effect biomarker levels, tobacco user behaviors and health status of natural adopters of several tobacco product classes (i.e., cigarettes, moist snuff, Camel Snus, dual use of cigarettes and Camel Snus, dual use of cigarettes and moist snuff) and of non-tobacco users. CSD0904 is discussed extensively in Sections 2.9.1.2, 2.9.2, 6.1.2.3.1.2 of the Camel Snus MRTPAs/PMTAs.

CSD0904 had a primary objective of determining multiple biomarkers of exposure (CSR, Table 5, p. 78; Table 7, pp. 96-101). A secondary objective was to analyze differences in biomarkers of exposure between the six enrolled cohorts. Camel Snus users reported being natural product adopters of Camel Snus 0.6 g Frost and Mellow and Camel Snus 1 g Winterchill flavored products. Data were pooled for all Camel Snus products.

Table 6.1.2-32 in the Camel Snus MRTPAs/PMTAs, reproduced in part below in Table 5, shows nicotine exposures in natural adopters of Camel Snus are lower than natural adopters of moist snuff.

Table 5: Nicotine Exposrues in Natural Adopters of Camel Snus (Table 6.1.2-32 Camel Snus MRTPAs/PMTAs, partial reproduction)		
Biomarker of Exposure (units)	**Moist Snuff (N=50)**	**Camel Snus (N=50)**
	Mean (Standard Deviation)	
NIC_{Eq}-T (µg/24 hr)	n=49 31969.9 (24096.7) [1]	n=50 12645.1 (11175.6)
NIC-U (ng/mL)	n=49 6.32 (4.37) [1]	n=50 3.57 (3.09)
COT-U (ng/mL)	n=49 384.17 (260.69) [1]	n=50 159.83 (134.84)
Statistically significant pairwise comparisons: [1] vs. Camel Snus Users. Source of table data is the CSD0904 CSR for all constituents except phenanthrene equivalents, naphthalene equivalents, acrylamide equivalents and urine mutagenicity, which were calculated in a post-hoc analysis (RDM PC 2016 274-a).		

Abuse liability of Camel Snus products

FDA recommends that MRTP applicants submit human studies "to assess the abuse liability and potential for misuse of the product as compared to other tobacco products on the market"[20]. In the context of tobacco products, abuse liability refers to the risk that use of a tobacco product will lead to psychological and/or physiological dependence, along with persistent product usage behaviors, development of tolerance and impeded ability to discontinue product use.[18] It is accepted that nicotine has a prominent role in the abuse liability of tobacco products.[17] It is also recognized that the manner of product use (i.e., inhalation during smoking vs. buccal absorption during oral use) and the product's formulation substantially determine its effects and abuse liability. Thus, tobacco and other nicotine products vary widely in their abuse liability. Part of evaluating an MRTPA is determining the proposed modified-risk product's abuse liability relative to other tobacco products (e.g., cigarettes). If the candidate MRTP is intended to reduce cigarette smoking, some of its characteristics and effects that contribute to abuse liability must remain sufficient for it to adequately substitute for the reinforcing effects of cigarettes.

Important product and clinical data related to the abuse potential of Camel Snus include its nicotine content and buffering, pharmacokinetic measures of nicotine exposure (i.e., peak plasma concentrations [C_{max}] and time to peak plasma concentration [T_{max}]), as well as systemic measures such as biomarkers of exposure to nicotine and its metabolites. Accordingly, the study data summarized in RJRT's MRTPAs/PMTAs specifically address nicotine exposure resulting from the use of Camel Snus, as

[20] Modified Risk Tobacco Product Applications. Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. pg 19.

compared to exposure from cigarette smoking. Additional discussion of the abuse liability of Camel Snus relative to cigarettes, including a discussion of published literature as well as quantitative and qualitative data produced by studies conducted by RJRT and others, is found in Camel Snus MRTPAs/PMTAs Section 6.1.6 and Henningfield et al. 2017.

Henningfield et al. 2017 (included in Section 7 of the Camel Snus MRTPAs/PMTAs), in their abuse liability assessment of the six Camel Snus products that are the subject of this Application, support the designation of all six products as MRTPs. After review of available data, the authors conclude that, based on the abuse liability profile of Camel Snus, it will serve as an acceptable and beneficial MRTP. This designation reflects the fact that the abuse liability of Camel Snus is substantially less than that of traditional cigarettes and likely higher than that of FDA-approved over-the-counter nicotine replacement therapy (NRT) medications.

Thus, Camel Snus is expected to benefit smokers who are concerned about the risks of smoking, but find medicinal NRT products unacceptable and who will continue to use some form of tobacco product. While the ultimate population impact of Camel Snus as an MRTP will depend on factors beyond abuse liability, Camel Snus appears to fall in the general "midrange" of nicotine product abuse liability, consistent with a potential to serve as a viable harm reduction product (see non-specific product discussion and illustrative graph in Niaura 2016).[21] A midrange harm reduction product is one that manifests low to moderate abuse liability and acceptability to current smokers, while also providing a substantial potential to reduce the risks that attend cigarette smoking.

Dissolution testing for smokeless tobacco products

As part of the response to this deficiency, RAIS presents dissolution experiments that provide information about the rate of release of nicotine and total nicotine released from Camel Snus products under specified laboratory conditions. Results of dissolution testing under specified laboratory conditions demonstrate good consistency both within and between manufacturing batches of product (3 batches, 3 replicates per batch of each designated Camel Snus product were tested). The small batch to batch variability observed within a given Camel Snus product is an indication that the products are manufactured consistently between batches and that the controls in place (e.g., for moisture, pH, etc.) are appropriate for the manufacturing of a consistent product. RAIS asserts that these dissolution data are for research purposes only and are not used to monitor quality control of the product. Dissolution results are not actionable specifications and are not used to make any decisions about batch release.

To date, there are no established methods to measure the release rates of constituents in smokeless tobacco products, including snus. Further, to date, there is no published Guidance or any form of

[21] Niaura R. Re-thinking nicotine and its effects. Schroeder Institute for Tobacco Research and Policy Studies. 2016.

communicated policy from the Center for Tobacco Products (CTP) on the subject. Indeed, on May 8, 2018, FDA published a combined synopsis/solicitation for a contractor to develop selective dissolution procedures for smokeless tobacco products.[22] This solicitation further demonstrates a lack of available methods from CTP for dissolution testing of constituents in smokeless tobacco.

While, to date, dissolution test methods are not available for smokeless tobacco products, dissolution testing is commonly used in the pharmaceutical industry to compare batches of oral drug delivery forms prior to clearance for distribution, as well as to test the quality of the product after certain changes are made (Shah 2005). Additionally, there have been several studies which indicate dissolution testing may be of utility in smokeless tobacco products.[23,24, 25] CDER issued Guidance for performing dissolution testing with additional Guidance on the comparison of dissolution profiles for different products to assess the safety and efficacy of pharmaceuticals in the absence of in vivo testing.[26,27,28,29]

Nicotine dissolution testing, as suggested by FDA in Deficiency 6 of this Advice and Information Request for Camel Snus products, is one option to "provide scientific evidence that the ranges that correspond to the high and low rejection limits [for Camel Snus products], and any other process controls, minimize the variability in the levels of nicotine released." Due to the lack of available standardized methods to conduct dissolution testing of smokeless tobacco products, RAIS worked with

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[22] See Solicitation Number: FDA-RFP-1194857, "Dissolution of Smokeless Tobacco Products," https://www.fbo.gov/index.php?s=opportunity&mode=form&id=d0dcf0ea0e1bed6dc51717d3e389a9a6 (accessed May 8, 2018)

[23] Miller, John H., et al "U.S. Pharmacopeia Dissolution Technique for the Determination of Nicotine and Flavor Release from Smokeless Tobacco Products." Presented at 2015 CORESTA Smoke-Techno Meeting Jeju, South Korea. https://www.coresta.org/sites/default/files/abstracts/2015_ST30_Miller_0.pdf (accessed June 8, 2018)

[24] Delvadia, P.R., et al. A biorelevant *in vitro* release/permeation system for oral transmucosal dosage forms. International Journal of Pharmaceutics 430 (**2012**) 104-113.

[25] Delvadia, P.R., Karnes, H.T. Selectivity investigation and liquid chromatographic method for the analysis of nicotine in tobacco extracts. Journal of Liquid Chromatography & Related Technologies. 36: 1849-1868, **2013**.

[26] Department of Health and Human Services, Food and Drug Administration (1995, November 30). Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation; Guidance. Accessed from: https://www.gpo.gov/fdsys/pkg/FR-1995-11-30/pdf/95-29218.pdf

[27] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: SUPAC-MR Modified Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation. September 1997. Accessed from: https://www.fda.gov/downloads/Drugs/Guidances/ucm070640.pdf

[28] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. September 1997. Accessed from: https://www.fda.gov/downloads/drugs/guidances/ucm070237.pdf

[29] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System: Guidance for Industry. December 2017. Accessed from: https://www.fda.gov/downloads/Drugs/Guidances/ucm070246.pdf

a contract research organization ("CRO"), (b) (4) to perform nicotine dissolution testing for products relevant to this deficiency. (b) (4)

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Camel Snus Robust (PM0000427/MR0000072)

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Camel Snus Mellow (PM0000428/MR0000070)

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Camel Snus Frost Large (PM0000429/MR0000069)

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Camel Snus Mint (PM0000430/MR0000071)

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Camel Snus Winterchill (PM0000431/MR0000073)

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(b) (4)

(b) (4)

(b) (4)

Camel Snus Frost (PM0000432/MR0000068)

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RAIS RESPONSE TO DEFICIENCY 6a

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RAIS RESPONSE TO DEFICIENCY 6b

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RAIS RESPONSE TO DEFICIENCY 6c

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RAIS RESPONSE TO DEFICIENCY 6d

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[30] U.S. Food and Drug Administration. Dissolution Methods. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getallData.cfm (Please see recommended conditions for dissolution for the Drug Name "Nicotine Prolacrilex".)

[31] Composition of CRP1, accessed via https://strp.wordpress.ncsu.edu/files/2017/01/CORESTA-CRP1-Composition.pdf

[32] Hatsukami et al. in *Topographical features of smokeless tobacco use,* 1988.

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RAIS RESPONSE TO DEFICIENCY 6e

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RAIS RESPONSE TO DEFICIENCY 6f

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[33] United States Pharmacopeia, Chapter <1088>. **2012**. Accessed from: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1088.html

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RAIS RESPONSE TO DEFICIENCY 6g

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RAIS RESPONSE TO DEFICIENCY 6h

(b) (4)

RAIS RESPONSE TO DEFICIENCY 6i

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RAIS RESPONSE TO DEFICIENCY 6j

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[34] United States Pharmacopeia, Chapter <711>. **2011**. Accessed from: https://www.usp.org/sites/default/files/usp/document/harmonization/gen-method/stage_6_monograph_25_feb_2011.pdf

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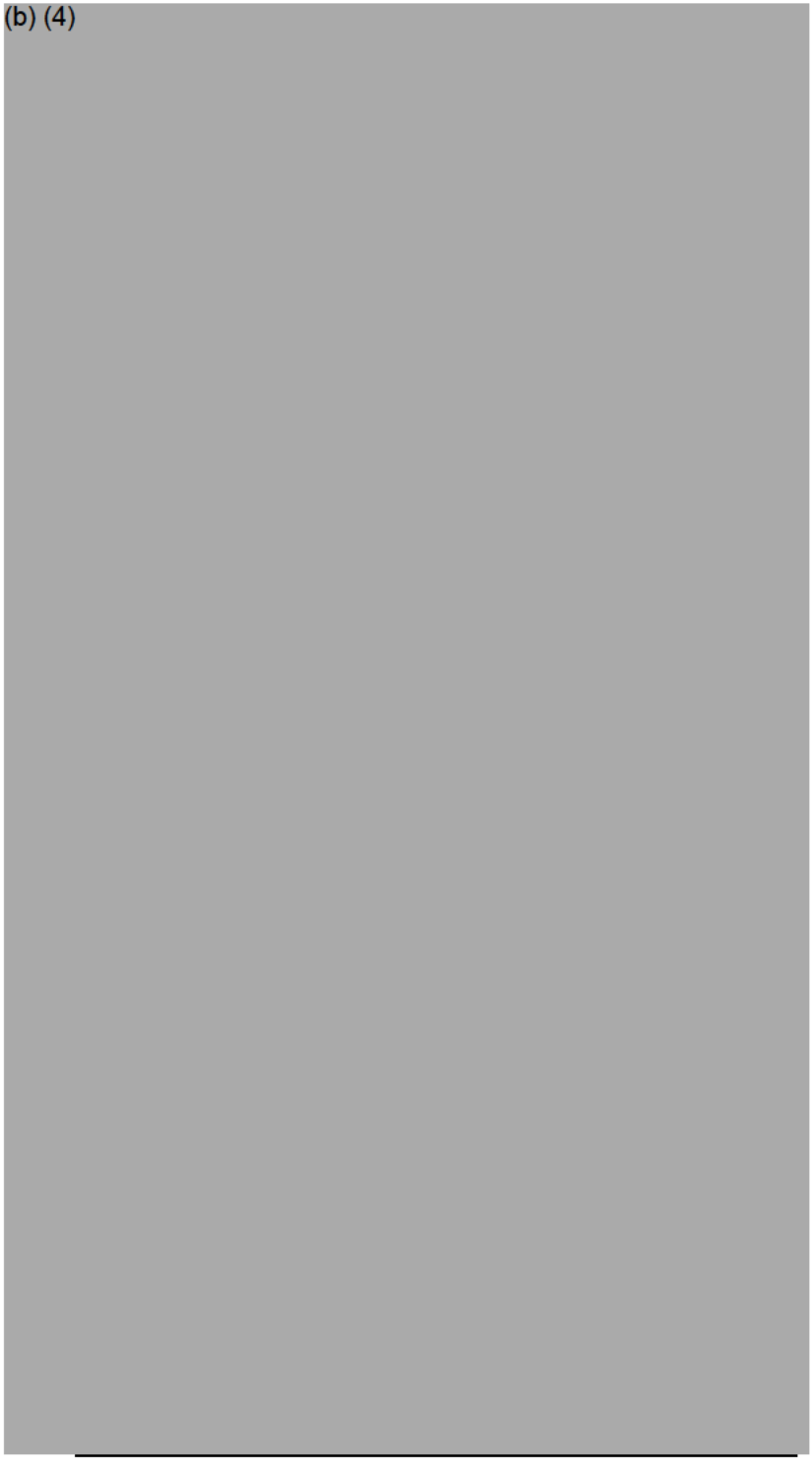

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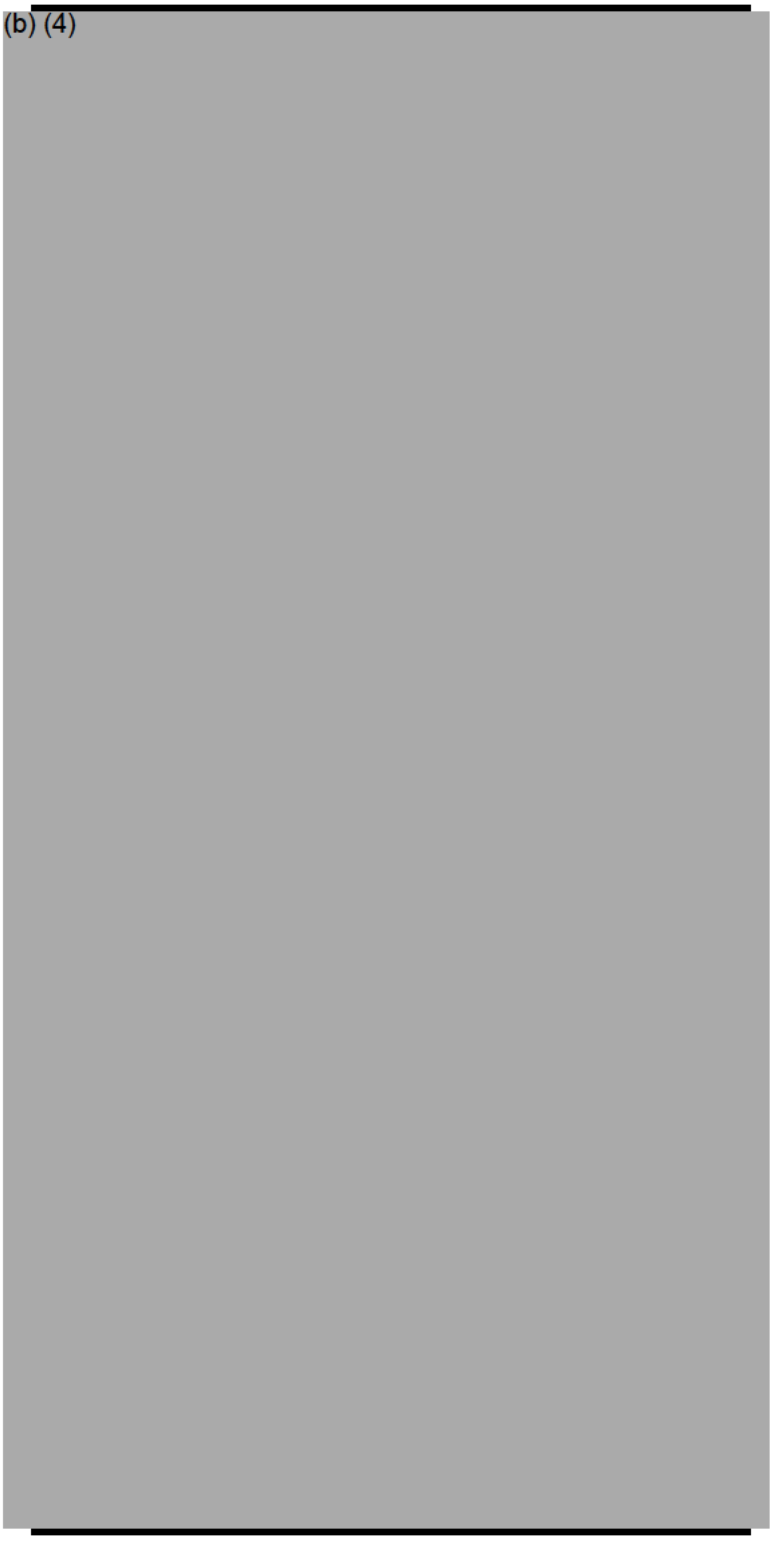

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As further discussed below, the utility of frozen conditions for the long term storage of commercial smokeless tobacco products and smokeless reference products is commonly practiced within the scientific community. The purpose of storing products under freezer conditions is to retard changes associated with storage of the product, thereby maintaining the characteristics of a product and thus rendering it suitable for research.

The CORESTA reference products (CRP) for smokeless tobacco products are currently stored, handled, and distributed for research purposes by North Carolina State University (NCSU) Tobacco Analytical Services Laboratory. CRP1, CRP2, CRP3, and CRP4 are housed in a "large walk-in freezer at NCSU Tobacco Analytical Services Laboratory" at -20 °C.[35] The recommended storage for these samples is for them to be "sealed in a plastic bag in a standard laboratory freezer at approximately -20 °C until analyses can be performed or the samples otherwise used. If this is not possible, the reference products should be refrigerated until needed for analysis."[35] These reference products are typically used in collaborative studies for smokeless tobacco research and can be used as quality control samples for method validation, and data quality assessment.

Various publications authored by the Center for Tobacco Products (CTP), the National Center for Toxicological Research (NCTR), and Centers for Disease Control (CDC) utilize a range of storage conditions for smokeless products tested for a variety of constituents/attributes. For example, CTP and the NCTR published in 2016 on the microbial populations in smokeless tobacco products where the smokeless tobacco products were stored in a zip-top bag at ambient conditions from time of purchase until time of analysis.[36] Products were purchased in 2012 and 2013 in two different locations; however, CTP and NCTR did not make it readily clear in the 2016 publication exactly how long the

[35] Smokeless Tobacco Reference Products Program: Sample Storage and Handling Protocols. Accessed from: https://strp.wordpress.ncsu.edu/files/2017/01/STRP.Sample.Handling.Storage.Protocols.pdf

[36] Han, J; Sanad, YM; Deck, J; Sutherland, JB; Li, Z; Walters, MJ; Duran, N; Holman, MR; Foley, SL. Bacterial Populations Associated with Smokeless Tobacco Products. Applied and Environmental Microbiology. 2016. 82(20): 6237-6283.

smokeless products were stored after purchase prior to analysis, or if CTP had conducted an evaluation of the storage conditions impact on the validity of their microbial population assessment.

In another example, CTP published on N-nitrosonornicotine (NNN) and total water content in smokeless tobacco products purchased in 2015.[37] Samples were purchased in January of 2015 and shipped at ambient temperatures within seven days of purchase to the laboratory for testing. A description of how the samples were stored prior to shipment was not given. Samples were stored at +4 °C upon receipt by the laboratory and stored for a month or more under these conditions prior to analysis for NNN and total water content, again without any evaluation of the impact these storage conditions may have had on the end result of NNN and total water content.

Additionally, the Centers for Disease Control (CDC) published a study in 1999 determining nicotine, pH, and moisture content of smokeless tobacco products.[38] Samples were stored at -71 °C until time of testing; once again, the time between purchase and analysis was not made clear. In a follow-up study, by the CDC in 2003, samples were purchased in 2001 and stored at -70 °C until shipment to a contract laboratory for analysis.[39] No mention is made of storage conditions at the laboratory after receipt, nor is the time difference between purchase and analysis given.

These examples demonstrate that even within federal regulatory agencies, including FDA/CTP, various storage conditions (including length of time between purchase and testing) have been used for the study of smokeless tobacco products. These examples of the utility of frozen conditions for long-term product storage support the use of samples stored in freezer conditions for extended periods of time to determine nicotine dissolution profiles.

RAIS RESPONSE TO DEFICIENCY 6k

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RAIS RESPONSE TO DEFICIENCY 6l

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[37] Amman, JR; Lovejoy, KS; Walters, MJ; Holman, MR. A survey of N'-nitrosonornicotine (NNN) and total water content in select smokeless tobacco products purchased in the United States in 2015. J. Agric. Food Chem. 2016, 64 (21), 4400-4406.

[38] Centers for Disease Control. Determination of Nicotine, pH, and Moisture Content of Six U.S. Commercial Moist Snuff Products -- Florida, January-February 1999. Morbidity and Mortality Weekly Report. May 21, 1999 / 48(19): 398-401. Accessed via https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4819a3.htm

[39] Richter, P; Spierto, FW. Surveillance of smokeless tobacco nicotine, pH, moisture, and unprotonated nicotine content. Nicotine & Tobacco Research. 2003. 5(6): 885-889.

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RAIS RESPONSE TO DEFICIENCY 6m

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RAIS RESPONSE TO DEFICIENCY 6n

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RAIS RESPONSE TO DEFICIENCY 6o

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RAIS RESPONSE TO DEFICIENCY 6p-6ee

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