



RAI Services Company

**James N. Figlar, Ph.D.**

Senior Vice President

Scientific & Regulatory Affairs

Winston-Salem, NC 27101

336-741-7818

Fax: 336-728-9062

figlarj@rjrt.com

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August 18, 2017

Benjamin Apelberg, Ph.D.  
Director, Division of Population Health 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 (ITEM 2) to July 25, 2017 INFORMATION REQUEST for MR0000068-MR0000073**

Dear Dr. Apelberg:

RAI Services Company ("RAIS")<sup>1</sup> 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") July 25, 2017, ADVICE/INFORMATION REQUEST letter regarding RAIS' submission of Applications Seeking a Modified Risk Tobacco Product Order ("MRTP Applications"), submitted under Section 911(d) of the Food, Drug, and Cosmetic Act ("FDCA") on March 30, 2017 for the following tobacco products:

- Camel Snus Frost (MR0000068);
- Camel Snus Frost Large (MR0000069);
- Camel Snus Mellow (MR0000070);
- Camel Snus Mint (MR0000071);
- Camel Snus Robust (MR0000072);
- Camel Snus Winterchill (MR0000073).

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<sup>1</sup> 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"), R.J. Reynolds Vapor Company, and Kentucky BioProcessing, Inc. ("KBP"). References to RAIS in this letter refer to itself and its affiliated companies where applicable.

This response refers to Item Two (2) in the aforementioned information request. Items not addressed in this document will be covered in separate responses. In this response, we have repeated CTP's requests, verbatim and in bold italics, followed by RAIS' 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,

A handwritten signature in black ink, appearing to read 'J. Figlar', with a large, stylized loop at the end.

James N. Figlar, Ph.D.  
Senior Vice President  
Scientific & Regulatory Affairs  
RAI Services Company

FDA-Listed Deficiencies and RAIS Response

2. ***All of your MRTPAs include a set of in vivo studies (TOX209, TOX210, TOX213, CN49730C, CN49730D, CN49730E, CN49730F, CN49730G) in Section 7\_3, all of which used a tobacco blend (blend of natural tobaccos ground to powder, with no preservatives or additives) and an aqueous extract of that blend for testing. You stated in Section 2, page 179, that “all six of the subject Camel Snus flavor styles are manufactured with an identical tobacco blend, so the findings of this series of in vivo studies on the Camel Snus blend and on an aqueous extract of that blend are relevant to all six flavor styles (Frost, Frost Large, Mellow, Mint, Robust, Winterchill).” All of these in vivo studies describe the estimation of group means, ANOVA, and statistical tests and include the data. Studies CN49730C and CN49730D describe the use of SAS for some analyses. However, we could not locate the programming code used to generate the statistical findings. Provide these materials for each study. If you have already provided this information, indicate the exact location within your MRTPAs.***

RAIS RESPONSE

Item Two (2) refers to a series of toxicology studies performed internally by RJRT and externally by the Battelle Life Sciences Research Center, and states that “we could not locate the programming code used to generate the statistical findings. Provide these materials for each study. If you have already provided this information, indicate the exact location within your MRTPAs.”

RAIS interprets this statement by FDA as a request for provision of additional information on the underlying programming code and software packages that were used to develop the statistical analyses of data for each of a series of in vivo studies of the Camel Snus tobacco blend and an extract of that blend. RAIS acknowledges that this information was not included in the original MRTPA submissions and provides below all available information responsive to the request.

The referenced studies are itemized in Table 1, which reproduces and enhances information provided in Table 6.1.4-2 of the Camel Snus MRTPA. The subject studies include some performed internally by RJRT (TOX209, TOX210, TOX213) and others externally by Battelle (CN49730C, CN49730D, CN49730E, CN49730F, CN49730G). The datasets and technical reports for all of these studies are included in Section 7 of the Camel Snus MRTPA, and are hyperlinked throughout that text. All studies, both internal RJRT and external Battelle, utilized a standard laboratory information system, Xybion Path/Tox Version 4.2.2, to capture, record and analyze the majority of study toxicology data. For some studies, additional software packages were used for certain statistical analyses, as noted by FDA and indicated in Table 1. Additional information regarding the context of the appended files to the referenced studies is provided immediately thereafter.

**Table 1. Index of RJRT *in vivo* studies [RJRT internal and Battelle external studies]**

<b>Study</b> [Conducted By]	<b>Title</b>	<b>Statistical</b> <b>Package(s)</b>	<b>Appended Files</b>
<b>TOX209</b> [RJRT]	Two Week Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Rats	Xybion Path/Tox Version 4.2.2	<a href="#">q02-xybion-pathtox-v422-algorithms</a>
<b>TOX210</b> [RJRT]	Two Week Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Mice	Xybion Path/Tox Version 4.2.2	<a href="#">q02-xybion-pathtox-v422-algorithms</a>
<b>TOX213</b> [RJRT]	Two Week Repeat Investigational Study of the Palatability of Smokeless Tobacco Blend and Extract Formulated in NTP-2000 Diets for Mice at Higher Doses	Xybion Path/Tox Version 4.2.2	<a href="#">q02-xybion-pathtox-v422-algorithms</a>
<b>CN49730C</b> [Battelle]	28-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats	Xybion Path/Tox Version 4.2.2; SAS Version 9.1	<a href="#">q02-xybion-pathtox-v422-algorithms</a> <a href="#">q02-cn49730c-scorecoding</a> <a href="#">q02-cn49730c-analysis</a>
<b>CN49730D</b> [Battelle]	28-Day Repeated Dose Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in CD-1 Mice	Xybion Path/Tox Version 4.2.2; SAS Version 9.1	<a href="#">q02-xybion-pathtox-v422-algorithms</a> <a href="#">q02-cn49730d-scorecoding</a> <a href="#">q02-cn49730d-analysis</a>
<b>CN49730E</b> [Battelle]	90-Day Repeated Dose Subchronic Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats	Xybion Path/Tox Version 4.2.2	<a href="#">q02-xybion-pathtox-v422-algorithms</a>
<b>CN49730F</b> [Battelle]	90-Day Repeated Dose Subchronic Toxicity Study of Tobacco Blend and Aqueous Tobacco Extract in CD-1 Mice	Xybion Path/Tox Version 4.2.2	<a href="#">q02-xybion-pathtox-v422-algorithms</a>

Study [Conducted By]	Title	Statistical Package(s)	Appended Files
<b>CN49730G</b> [Battelle]	2-Year Chronic Toxicity/ Carcinogenicity Feeding Study of Tobacco Blend and Aqueous Tobacco Extract in Wistar Han Rats		
	12-Month Repeated Dose Chronic Toxicity Study	Xybion Path/Tox Version 4.2.2	<a href="#">q02-xybion-pathtox-v422-algorithms</a>
	1-Year Time Point: Histopathological Evaluation of All Groups	SAS Version 9.2	<a href="#">q02-epl1yrhistodatafemalesmales-06042014</a>
	2-Year Chronic Carcinogenicity Study	Xybion Path/Tox Version 4.2.2; STATA 11	<a href="#">q02-xybion-pathtox-v422-algorithms</a> <a href="#">q02-battelleletter-cn49730g-statsanalysisreport</a>

The Xybion Path/Tox Version 4.2.2 software was used in all of the studies to capture and statistically analyze the majority of toxicology findings. The associated file, q02-xybion-pathtox-v422-algorithms, appended in Table 1 contains proprietary Information belonging to Xybion Medical Systems Corporation, 240 Cedar Knolls Road, Cedar Knolls, New Jersey 07927-1698 (www.xybion.com ), which the vendor specifies “is to be handled in a "Company Confidential" manner in accordance with the PATH/TOX SYSTEM License and Service Agreement or the PATH/TOX SYSTEM Software Evaluation Agreement.” Accordingly, neither RJRT nor RAIS possesses or have access to the underlying proprietary programming code. However, this file presents all of the algorithms that are used by the Xybion software.

Studies CN49730C and CN49730D utilized SAS Version 9.1 software to analyze neurobehavioral and functional observational battery (FOB) endpoints, as described in the final reports. Appended files in Table 1 associated with the aforementioned studies include programming code to establish categorical values related to observations and programming code used to generate statistical findings.

Study CN49730G, in addition to the statistical evaluations performed by the Xybion software, utilized SAS Version 9.2 and STATA 11 software programs to analyze tumor data. Statistical analysis of tumor incidence data from the 1-year time point of this study was performed using SAS Version 9.2 software and relevant programming code is appended in Table 1. The STATA statistical software was used for the analysis of tumor data for the 2-year chronic carcinogenesis bioassay of this study. A February 29, 2012 Battelle memorandum to the study file, as appended in Table 1, provides details on the use of STATA software in the analysis of tumor data for this study. Coding relevant to the statistical analysis performed using STATA software is included in Attachment 2 of this memorandum.