

## ***HRRC PROPOSAL***

To: Mike Ogden  
HRRC Chairperson

Date: August 20, 2009

From: Elaine Round, Sheri Bowman, Kelly Harger, Mitch Stiles

Subject: Assessment of the Nicotine Contribution from the Modern Smoke-Free Tobacco Product Portfolio (HRRC Proposal #0906)

**A. Background** - R. J. Reynolds Tobacco Company (RJRT) is aggressively pursuing harm reduction efforts in its tobacco products portfolio. These efforts include the development and launch of modern smoke-free tobacco (MSFT) products, which currently include Camel Dissolvables and Camel Snus. Camel Dissolvables are tobacco products made primarily of finely milled tobacco that are designed to be completely consumed in the mouth without the need for spitting. Camel Orbs, Camel Strips, and Camel Sticks are examples of Camel Dissolvables. Camel Snus is a pouched, moist snuff product composed of pasteurized tobacco with a low sodium and moisture content. Similar to Camel Dissolvables, spitting is not required while using snus, allowing MSFT products to be used discreetly in places that do not allow smoking.

Previous RJRT studies examined the use of MSFT products by human participants throughout a three-week product transition from exclusive, *ad libitum* use of usual brand (UB) cigarettes to dual use of one MSFT product concurrent with a 75-100% reduction goal in cigarette consumption. Separate studies were conducted with each MSFT product. Those studies evaluated several aspects of the tobacco transition, including product usage, biomarkers of tobacco exposure in blood and urine, and subjective responses to questionnaires. The studies involving Camel Strips and Camel Sticks included in-lab product use with the collection of blood samples just prior to and for 60 minutes following initiation of product use. The study in which participants used Camel Snus extended the collection of blood samples to 90 minutes following the initiation of product use. Serum nicotine concentrations were measured in the timed blood samples in an effort to understand the timing and level of nicotine uptake from this new class of products. Results have been obtained for serum nicotine levels following Strip and Stick use, but are still pending for the study employing Camel Snus.

Results from the analyses performed to date showed a steady decline in serum nicotine levels for 60 minutes following use of a single Strip or Stick in the lab setting. One probable reason for this observation was the protocol requirement for participants to abstain from tobacco use for only 30 minutes prior to their study visit. Since the typical half-life of nicotine in the blood is 30-120 minutes, only a portion of the nicotine present at the start of this abstinence would be cleared from the blood before participants used

product during the test session. As a result, participants averaged serum nicotine concentrations of approximately 13ng/mL just prior to product use in the lab setting. The clearance of this nicotine from the blood concurrent with nicotine uptake from Strip or Stick use still resulted in an overall decline in nicotine concentrations following MSFT use.

In an attempt to determine the serum nicotine contribution from in-lab MSFT use, the average rate of serum nicotine clearance across all participants was applied to each participant's starting nicotine concentration to estimate the clearance of the initial nicotine levels over time. Calculated values of remaining initial nicotine at each time point were subtracted from observed values to determine corrected concentrations that theoretically correspond to the nicotine absorbed specifically from Strip or Stick use. These corrections did indicate a serum nicotine increase resulting from Strip or Stick use; however, the validity of the half-life estimation on which the corrections are based is unknown.

Additionally, the time at which the maximum nicotine concentration occurred following product use could not be determined from the available data. The corrected nicotine concentrations still appeared to be rising 60 minutes following the initiation of Strip and Stick use in lab. Although we extended the time of blood collections following initiation of Snus use to 90 minutes, results are not yet available for comparison. To clarify the validity of the correction method described above and to determine the time at which peak nicotine concentrations occur following product use, a separate study employing a longer tobacco abstinence period and an extended period of timed blood sample collection is required.

**C. Human Participants** – Serum nicotine levels, carboxyhemoglobin saturation, and tobacco abstinence symptoms can only be assessed with human tobacco users as participants.

**D. Product Integrity** – All MSFT products to be tested are current market products. Product Integrity Stewardship has approved this study (Attachment 1).

**E. Tobacco Products** – Participants will include smokers of Full Flavor Low Tar (FFLT) cigarettes of any type. Smoke yield ranges for FFLT cigarettes using a Cambridge filter method with puffs of 35 mL occurring every 60 seconds, 2 seconds in duration are shown below:

	'Tar' mg/cig	Nicotine mg/cig	Carbon Monoxide mg/cig
Usual Brands (range)	7.0 - 13.1	0.56 – 1.04	5.8 – 15.7

[Data taken from TITL Market Sample 51 Final Report, January 27, 2009].

### UB Cigarettes

At the screening visit, participants will provide study staff with one pack of their usual brand of cigarettes. Study staff will copy the front and return the pack to the participant. At Test Session 1, participants will provide the study staff with one usual brand cigarette that staff will dispense to the participant to smoke in the lab.

### MSFT Products

The MSFT products to be tested in this study include Camel Snus (Frost and Mellow), Camel Orbs (Fresh and Mellow), Camel Strips (Fresh), and Camel Sticks (Mellow). All products are currently available in the marketplace. Following completion of the screening oral exam and fulfillment of all inclusion and no exclusion criteria, participants will receive a trial pack containing one of each product and variety to sample during the week prior to Test Session 1. At the end of Test Session 1, participants will receive a 6-unit supply of the product to which they are randomized for use during their next study visit. Participants will also receive instructions for use and will be asked to use 1 unit per day according to instructions to become accustomed to using each product prior to in-lab use. During Test Sessions 2-5, participants will use 1 unit of the MSFT product that was provided to them for use over the previous week. In the case of Camel Snus and Camel Orbs, participants will be asked to choose one variety to take home with them. They will be presented with the same variety in the lab during their test session.

### Product Use Instructions

For each product, participants will not be permitted to eat or drink until the product has completely dissolved or has been removed in the case of snus. Participants will also be asked not to spit during or after use of each product. Use of all products in the lab will be timed to determine duration of use.

#### Camel Orbs

Participants will be asked to use one Orb to completion by placing the Orb between their cheek and gum and occasionally moving to a different location in the mouth during use.

#### Camel Strips

Participants will be asked to use one Strip to completion by placing the Strip on the top of the tongue/roof of mouth or by folding and placing between the lip and gum.

#### Camel Sticks

Participants will be asked to use ½ of a Stick to completion by placing the Stick portion between their cheek and gum and occasionally moving to a different location in the mouth during use.

#### Camel Snus

Participants will be asked to place one pouch between either upper or lower lip and gum and to leave in place for a minimum of 15 and a maximum of 30 minutes. Occasional movement of the pouch will be suggested, but not required.

***F. Procedures for Participant Selection*** – Bellomy Research of Winston-Salem will recruit participants for this study. Volunteers who meet the following criteria will be included in the study:

1. Males or females age 21-55, inclusive
2. Weighs at least 110 pounds
3. Is in generally good health
4. Smokes 10-30 cigarettes per day and inhales the smoke
5. Primary tobacco use is smoking cigarettes
6. Smokes FFLT combustible cigarettes, 85s or 100s, menthol or non-menthol
7. Is not postponing a decision to quit smoking to participate in study
8. Has prior experience using smokeless or dissolvable tobacco products, but does not currently use habitually
9. Has not given a whole blood donation in at least 8 weeks (56 days)

The following will exclude participants from the study:

1. Has current oral lesion(s) as determined by the medical advisor or designee
2. History of heart disease, kidney disease, asthma or any other lung disease, diabetes, uncontrolled hypertension, liver disease, neurological disease, or psychiatric illness.
3. Hemoglobin below 12.5 g/dL
4. Positive for HIV, Hepatitis B, or Hepatitis C
5. Hemophilia or any other bleeding disorders
6. Clotting disorders with concomitant use of anticoagulants
7. Women who are pregnant, breastfeeding, or have given birth in the last 12 months
8. Body mass index (BMI) > 40
9. History of illegal IV drug use
10. Drinks more than 14 alcoholic beverages per week
11. Employed by a tobacco company, a sub-contractor of a tobacco company, or handles tobacco as part of their job
12. Current diagnosis of peptic ulcers or irritable bowel syndrome
13. Current use of nicotine replacement products or intention to use nicotine replacement products during the course of the study
14. Afternoon exhaled CO measurement of <15ppm at screening visit

Participants who meet all the inclusion criteria and none of the exclusion criteria are eligible to be randomized/enrolled into the study. Fifteen participants and up to 15 alternates will be included in the study. The 15 alternates who meet all the inclusion and none of the exclusion criteria will be included through the end of the first test sessions. If a participant's expired CO levels are >10 ppm at the beginning of Test Session 1, that participant will be excused from the study and an alternate will be invited to participate. If that alternate's expired CO level is ≤10 ppm, the alternate will become a participant and will be included in the remainder of the study.

If a participant's expired CO levels are >10 ppm at any single test session after Test Session 1, the participant will be excused from that test session and asked to attend a make-up test session the week following Test Session 5. If a participant's expired CO levels are >10 at any two test sessions after Test Session 1, that participant will be excused from the study.

**G. Participant Handling** – Potential participants will be invited to attend a screening visit to introduce them to the study requirements. We will provide information about tobacco abstinence requirements, what to expect at test sessions, the products to be tested, and instructions for use. For those interested, we will obtain informed consent. Following consent, medical history and demographic information will be obtained, participants will complete the Fagerström Test for Nicotine Dependence (FTND) and Mood and Physical Symptoms (MPSS) questionnaires and will have a screening oral exam and hemoglobin screening to determine final eligibility. Once enrolled, participants will report to our offsite testing facility one day per week for five consecutive weeks. Eligibility for each test session will be determined by expired CO levels. (See Section F. Procedures for Participant Selection) Each test session will last approximately 3.5 hours. Following Test Session 5, participants will have a final oral exam. Screening and final oral exams will be performed by a medical professional (NP, MD, or DO). Participants will receive a maximum compensation of \$1490 for their time and travel to the orientation and 5 successful test sessions [Orientation = \$85, Test Sessions 1-5 = \$275 each, Final Oral Exam = \$30]. Alternates who are not asked to participate will be compensated \$50 for the time and travel necessary to attend Test Session 1. Participants whose expired CO levels are >10 ppm at any test session will be compensated \$50 and treated according to protocol.

**H. Procedures For Study Visits** – Following the screening visit, eligible participants will report to the test facility for one test session per week for five consecutive weeks. Test sessions will be conducted Monday through Friday mornings.

Participants will be required to abstain from all tobacco and nicotine use for 12 hours prior to each test session. To facilitate tobacco and nicotine abstinence, participants will be asked to end use of tobacco/nicotine at 8:30 p.m. the evening prior to their test session and will be asked to report to the test facility at 8:30 the next morning. At the start of each session, participants will be asked what time they finished using their last nicotine-containing product. Smoking abstinence will be confirmed by measuring the amount of carbon monoxide in participants' expired breath at the start of each study visit. Participants must register an expired CO level of  $\leq 10$  ppm at the start of each test session to participate further that day.

Blood samples will be collected via an indwelling IV catheter inserted in the antecubital region of the forearm or the hand once the expired CO eligibility has been met at each test session. Blood samples for serum nicotine/cotinine analysis will be collected at -2, 0, 3, 5, 7.5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 minutes with

respect to initiation of product use. Blood samples will be collected to measure carboxyhemoglobin saturation at -2, 30, and 60 minutes with respect to initiation of product use. The total volume of blood to be drawn at each test session is approximately 88mL. For the entire study, a total of approximately 440mL of blood will be drawn, just less than one pint.

Samples to be analyzed for nicotine and cotinine will be collected in serum separator tubes, allowed to sit for at least 30 minutes, and will be centrifuged at 3000 rpm for 20 minutes at 8°C. Serum will be aliquoted, frozen at -70°C, and shipped to an outside lab for analysis.

Samples to be analyzed for carboxyhemoglobin saturation will be collected in tubes containing EDTA. Whole blood will be analyzed within 20 minutes of sample collection using a CO-oximeter.

The cigarette filter remaining after UB smoking in the lab at Test Session 1 will be collected for yield-in-use analysis of nicotine. Butts will be processed by clipping off a 1 cm portion from the mouth end. Each 1 cm tip will be stored in a separate amber glass jar, frozen at -70°C and shipped to an outside lab for analysis.

The snus pouch used by each participant in the lab will be collected and analyzed for the amount of remaining nicotine. Each pouch will be placed in a separate amber jar, frozen at -70°C, and shipped to an outside lab for analysis.

The MPSS will be administered  $\leq 10$  minutes prior to the start of product use, and at 5, 15, 30, 45, 60, 90, 120, 150, and 180 minutes following product use to assess tobacco abstinence symptoms.

***I. Forms, Questionnaires and Written Instructions*** – Forms and questionnaires to be used include: the informed consent form (Attachment 2), a demographic information form, a medical history form (Attachment 3), the FTND (Attachment 5), the MPSS (Attachment 6), and product usage logs (Attachment 7). Participants will also be given a card with phone numbers to call in case of questions or concerns (To be submitted when medical advisory contract is finalized). Written instructions will be given regarding product use (Attachment 4).

***J. Personal Information*** – Prior to or when they arrive at the test site, Bellomy Research will assign a unique alphanumeric identifier to each participant. All hardcopy or computer data records for each participant will contain only the identifier. The signed informed consent and medical history forms will be retained in a secure location at the offsite testing facility. At the conclusion of the study the records will be transferred to secure records retention for archival purposes. All information contained on the informed consent and medical history forms will remain confidential.

***K. Staff Training*** - At least one staff member working at the offsite facility is certified to perform CPR. All staff members have been certified by the American Red Cross to

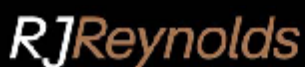
properly handle biological samples to protect themselves and others from exposure to bloodborne pathogens. In addition, all staff members will follow Occupational Safety and Health Administration (OSHA) safety guidelines pertaining to Occupational Exposure to Bloodborne Pathogens when handling biological samples. All biohazard waste generated during this study will be disposed of in accordance with OSHA guidelines. RJRT study staff has been trained to properly maintain the confidentiality of study participants, including their personal identity and all personal health information.

Certified, trained LPN or RN phlebotomists will be contracted from an outside source for this study. Certification of the contracted phlebotomists participating in this study will be documented. Training for study-specific procedures will be performed by a certified RJRT staff phlebotomist, and at least one RJRT staff phlebotomist will be on site during study procedures to assist and supervise the contracted phlebotomists.

Oral exams and medical advisory will also be contracted from an outside source for this study. Oral exams will be performed by a licensed nurse practitioner (NP), physician assistant (PA), medical doctor (MD), or doctor of osteopathic medicine (DO). Medical advisory will be provided by a licensed MD or DO.

---

**Keywords:** COHb, expired CO, MSFT, Orbs, questionnaires, SAU, serum nicotine, serum cotinine, Strips, Sticks, snus, tobacco abstinence, UB, usual brand, YIU



## Inter Office Memo

### **Product Integrity Stewardship**

**SUBJECT:** Assessment of Serum Nicotine  
Exposure from Modern Smoke-  
Free Tobacco Products  
(HRRC Proposal #0906)

**DATE:** August 20, 2009

**TO:** Dr. Mike Ogden, Ms. Elaine  
Round, Mr. Mitch Stiles

**FROM:** Ryan J. Potts

#### **Summary**

Stewardship has reviewed a proposal to study serum nicotine concentrations following use of several Modern Smoke-Free Tobacco Products (MSFTPs). Based on a review of all available information, Stewardship approves the specific testing detailed in the protocol (Protocol CSD0914/HRRC Proposal #0906).

This proposal requires review by the Human Research Review Committee (HRRC). This recommendation does not constitute approval for any other human studies of these products without further review by Stewardship.

#### **Background**

The purpose of the proposed study is to obtain information on serum nicotine concentrations following use of several MSFTPs, namely CAMEL Orbs (fresh and mellow), CAMEL Strips (fresh), CAMEL Sticks (mellow) and CAMEL Snus (frost and mellow). Secondary objectives of this study are to i) assess tobacco abstinence symptoms prior to and 3 hours following initiation of product use after a 12-hour tobacco and nicotine abstinence, and ii) assess carboxyhemoglobin levels prior to and 1 hour following initiation of product use.

The MSFTPs being tested in the study are all currently marketed products. Up to 15 participants will be included in the study. Participants will include both males and females, ages 21-55, who are current smokers of 10-30 full-flavor light cigarettes/day. Participants will abstain from tobacco/nicotine use for 12 hours prior to each of 5 weekly study visits. One MSFTP or usual brand cigarette (UB) will be used by each participant per visit. Blood will be collected over the course of 3 hours just prior to and following product use to assess the serum nicotine concentrations and carboxyhemoglobin levels at various time points. Questionnaires will be administered to assess tobacco abstinence symptoms.



**INFORMED CONSENT CHECKLIST**

**Assessment of Serum Nicotine Exposure from Modern Smoke-Free Tobacco Products**

HRRC #0906

CSD0914

September 10, 2009

**Study Sponsor: R.J. Reynolds Tobacco Company (RJRT)**

- \_\_\_\_ YOU STATE THAT YOU ARE AT LEAST 21 YEARS OF AGE.
- \_\_\_\_ YOU HAVE VOLUNTARILY AGREED TO BE PART OF THIS RESEARCH STUDY. NOBODY HAS PRESSURED YOU TO TAKE PART IN IT.
- \_\_\_\_ You are not postponing a decision to quit smoking just to take part in this study.
- \_\_\_\_ You should not make other blood donations while taking part in this study.
- \_\_\_\_ You understand that you can ask questions at any time if there is something in this form you do not understand.
- \_\_\_\_ You are aware of the Surgeon General's warnings concerning cigarette smoking:
- Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.
  - Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
  - Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.
  - Cigarette Smoke Contains Carbon Monoxide.
- \_\_\_\_ You understand the following warnings concerning use of oral tobacco products:
- This Product is not a Safe Alternative to Cigarettes.
  - This Product May Cause Gum Disease and Tooth Loss.
  - This Product May Cause Mouth Cancer.

## Attachment 2

- \_\_\_\_\_ All samples collected from you and all data pertaining to you will be identified only by a code number. The link between the code and your identity will be maintained *in strictest confidence*. Documentation that contains your identity, including this consent form and medical history information, will be kept in a secure location with access limited to study staff and the medical practitioners contracted for this study. Any reports or publications resulting from the data collected in this study will not identify you by name.

### WHY THIS STUDY IS BEING DONE

- \_\_\_\_\_ This research study will collect information to help understand the nicotine levels taken up in the blood following modern smoke-free tobacco product use. This study will also look at any symptoms you might experience after 12 hours free from tobacco and nicotine use and after study product use in the lab setting.
- \_\_\_\_\_ The blood samples to be collected will be used to determine the amounts of carbon monoxide, nicotine, and related compounds in your body as a result of using tobacco products.
- \_\_\_\_\_ The expired breath samples will provide a measure of the amount of carbon monoxide you have absorbed as a result of smoking and other environmental factors.
- \_\_\_\_\_ The filter from the cigarette you smoke in the lab will be collected and used to determine the amounts of 'tar' and nicotine trapped by the filter during smoking.
- \_\_\_\_\_ The snus pouch you use in the lab will be collected and used to determine the amount of nicotine remaining in the pouch after use.
- \_\_\_\_\_ Up to 15 participants and 15 alternates will be recruited for this study.

### YOU UNDERSTAND THE FOLLOWING:

- \_\_\_\_\_ This study is for research purposes and is not intended to treat any medical condition.
- \_\_\_\_\_ You state that you smoke 10 - 30 cigarettes each day and inhale the smoke.
- \_\_\_\_\_ You state that your primary tobacco use is smoking cigarettes.
- \_\_\_\_\_ You will continue to use the same style of usual brand cigarette throughout this study – one example might be Camel Light, king size, non-menthol, hard pack.
- \_\_\_\_\_ You will use only your usual brand cigarettes or the study products provided to you and will not use any other tobacco- or nicotine-containing products during the course of this study. Examples include other cigarettes, pipe tobacco, chewing tobacco, cigars, other moist or dry snuff, nicotine chewing gum, nicotine lozenges, nicotine spray, or a nicotine patch.

## Attachment 2

- \_\_\_\_\_ You agree to provide the study staff with an accurate medical history and list of medications you are currently taking. It is important that you provide information about your health that is accurate and true. Failure to provide important medical information or not truthfully reporting medical information could put you at risk if you are selected to participate in this study. Study staff will review with you the information you provide for accuracy.
- \_\_\_\_\_ You agree to have a brief oral cavity (mouth) examination by a trained medical professional before acceptance into the study and again at the end of the study.
- \_\_\_\_\_ You will report to the research facility (here) for a screening visit, five test sessions that will last about 3.5 hours each, and one final visit for an oral exam lasting about 10 minutes.
- \_\_\_\_\_ If you are chosen to be a participant, your eligibility for each test session will be determined by the amount of carbon monoxide measured in your breath at the start of each visit. If the amount is higher than a designated cutoff at Test Session 1 **for whatever reason**, you will be dismissed from the remainder of the study. If the amount is higher than a designated cutoff at any single test session after Test Session 1, you will be excused from that test session, and you will be provided with one opportunity to make up that session after the last week of the study. If the amount is higher than the cutoff at two test sessions following Test Session 1, you will be dismissed from the study.
- \_\_\_\_\_ If you are chosen to be an alternate, you will be asked to follow all study procedures prior to Test Session 1 and to report to the test facility ready to complete Test Session 1 if a position becomes available. If a position becomes available and the amount of carbon monoxide measured in your breath is below the designated cutoff, you will be invited to become a participant. If no position is available for Test Session 1, you will be excused from the study.
- \_\_\_\_\_ You will stop smoking and discontinue use of all nicotine-containing products at 8:30 the evening before each study visit. Starting at that time, you will not use any tobacco- or nicotine-containing products until you are asked to do so during your test session the following morning.
- \_\_\_\_\_ You will provide blood samples, an expired breath sample and will complete questionnaires at each test session.
- \_\_\_\_\_ At each test session, you will have a catheter inserted into your arm or hand after the carbon monoxide levels in your breath have been determined to be below the designated eligibility cutoff. The catheter will remain in place throughout the test session.
- \_\_\_\_\_ There may be discomfort when the needle is placed and withdrawn. As with any needle stick or skin breakage, there is a risk of infection, tissue damage, and bleeding. Sterile procedures will be used to limit these risks.
- \_\_\_\_\_ Up to 21 tubes of blood will be collected during the course of each test session. The volume of blood drawn at each session will be approximately 88 mL, which is equivalent to 3 fluid ounces or approximately 1/3 cup. The total volume of blood

## Attachment 2

drawn during the entire study will be approximately 440 mL, which is just less than 1 pint or 2 cups.

\_\_\_\_\_ At Test Session 1, you will smoke one usual brand cigarette that you will provide to the study staff.

\_\_\_\_\_ At Test Sessions 2, 3, 4, and 5, you will use one modern smoke-free tobacco product that will be randomly assigned each week. You will use each product following the instructions below:

Tobacco Orbs: You will use one Orb to completion by placing it between your cheek and gum and occasionally moving it to a different location in your mouth during use.

Tobacco Strips: You will use one Strip to completion by placing it on the top of your tongue, roof of your mouth, or folding it and placing it between your lip and gum.

Tobacco Sticks: You will use ½ of a Stick (the entire portion provided to you) to completion by placing it between your cheek and gum and occasionally moving it to a different location in your mouth during use.

Camel Snus: You will place one snus pouch between either your upper or lower lip and gum and leave it in place for a minimum of 15 minutes and a maximum of 30 minutes. Occasional movement of the pouch is suggested, but not required.

Additional instructions for all products:

You will not be permitted to spit during or after product use in the lab setting.  
You will not be permitted to eat or drink while using product in the lab setting.

\_\_\_\_\_ You must follow the study protocol for each week of the study if you decide to participate:

- You must stop all tobacco and nicotine use at 8:30 the evening before your test session.
- You must use the study product given to you in each test session according to instructions.
- You will be given a 6-day supply of the modern smoke-free product you will use in your test session the following week. You must use the provided modern smoke-free product, according to instructions, one per day for the first 6 days of the 7-day period before each test session.

\_\_\_\_\_ You will be required to maintain a daily tobacco product usage log throughout the study and to return it at each test session, along with any unused study product.

\_\_\_\_\_ You must honestly and **accurately** record your **actual** tobacco product use patterns throughout the study.

\_\_\_\_\_ If you do not complete all study requirements (which include tobacco use as outlined above, returning the tobacco product log and/or any unused study product, and fulfilling visit procedures), you will not receive full study payment and may only be paid for test sessions properly completed to date.

## Attachment 2

- \_\_\_\_\_ You may be dismissed from the study by the study director for various reasons, including but not limited to illness, failure to report to the test session on time, and violations of study protocol (for example, smoking cigarettes other than usual brand, not returning the tobacco product log, not abstaining from tobacco use for 12 hours prior to test sessions).
- \_\_\_\_\_ You understand that as with any tobacco product, Tobacco Orbs, Sticks, Strips, and Camel Snus are meant solely for the enjoyment and use of adult tobacco consumers. You understand these products are meant **only** for **your** use and you take responsibility for keeping them in your possession and control.
- \_\_\_\_\_ You will **not** place study products in a location where they would be available to **minors** at any time.
- \_\_\_\_\_ The study products are not intended to cause side effects; however, in addition to the warnings listed above, some participants in previous studies reported experiencing the following symptoms during their participation: hiccups, nausea, heartburn, mouth and gum irritation.
- \_\_\_\_\_ All participants and alternates will be compensated \$85 for the screening visit and \$30 for the final oral exam. Participants will be compensated \$275 for each completed test session. Alternates who are not invited to become participants will be compensated \$50 for the time and travel required to attend Test Session 1. Participants whose expired carbon monoxide measures higher than a designated limit will be compensated \$50 for the time and travel required for that specific test session. Total possible study compensation for the screening visit, five successful test sessions, and completion of the final oral exam will be \$1490 for the time and travel necessary for participation.
- \_\_\_\_\_ In the unlikely event of a laboratory accident (such as broken blood tubes or an accidental needle stick of lab personnel), you consent to have another blood sample drawn to test your blood for the Hepatitis B virus surface antigen and antibodies to the Hepatitis C virus and HIV, the virus that causes AIDS. These tests will be to ensure that lab personnel have not been exposed to potential blood-borne diseases. You will be notified of any such requirement and agree to return upon reasonable notice and at a convenient time and place to have further blood testing performed.

Do you have any questions?                      YES \_\_\_\_\_                      NO \_\_\_\_\_

### **YOU UNDERSTAND THAT YOUR INVOLVEMENT IN THIS STUDY INCLUDES THE FOLLOWING:**

- \_\_\_\_\_ Prior to signing this consent form, you state that you will notify study staff of any other forms of tobacco or nicotine you use besides cigarettes.
- \_\_\_\_\_ You state that you do not use any illegal (including intravenous) or non-therapeutic drugs.
- \_\_\_\_\_ You state that you do not drink more than 14 servings of alcoholic beverages per week (1 serving = 12 oz beer, 6 oz wine, or 1 oz hard liquor).

## Attachment 2

- \_\_\_\_\_ You state that you will not drink more than 2 servings of alcoholic beverages the night before your test session.
- \_\_\_\_\_ (WOMEN ONLY) You must not participate in the study if you are breastfeeding, pregnant, have given birth in the last 12 months, or are planning to become pregnant during the course of the study.
- \_\_\_\_\_ You do not work in an occupation where you regularly handle tobacco in a hands-on manner.
- \_\_\_\_\_ Whether you can be a part of this study depends upon all the information you have provided in this form and the medical history information you will provide if you consent to participate in this study. You will not be officially accepted for participation in this study until your medical history has been reviewed and approved by a medical professional.
- \_\_\_\_\_ You can address any questions you have to the personnel performing the study before signing this form. After the study begins, if you have any questions regarding scheduling, study instructions, study products or supplies, call the study staff at pager number 336-750-5940. For medical concerns related to the study, call the pager number for Clinical Trials of America at 336-806-1600. When they return your page, please identify yourself as a participant in the R.J. Reynolds tobacco study. Clinical Trials of America is located at 215 Executive Park Blvd., Winston –Salem, NC 27103.
- \_\_\_\_\_ You are free to withdraw from the study at any time.
- \_\_\_\_\_ In signing this consent form, you confirm that you have answered all the questions accurately and you know of no reason why you should not participate in this study.

Do you have any questions? YES \_\_\_\_\_ NO \_\_\_\_\_

\_\_\_\_\_  
Participant (PRINT NAME)

\_\_\_\_\_  
Participant Signature

Date: \_\_\_\_\_

Time: \_\_\_\_\_

\_\_\_\_\_  
Person Administering Consent (PRINT NAME)

\_\_\_\_\_  
Person Administering Consent (Signature)

Date: \_\_\_\_\_

Time: \_\_\_\_\_

**Participant #** \_\_\_\_\_  
**Participant ID** \_\_\_\_\_  
**Date** \_\_\_\_\_  
**Year of Birth** \_\_\_\_\_ **Age** \_\_\_\_\_

**MEDICAL HISTORY FORM**  
*To be completed by study staff*

- Height: \_\_\_\_\_ ft \_\_\_\_\_ in
- Weight: \_\_\_\_\_ lbs      BMI: \_\_\_\_\_ (>40 excludes)

<b>PERSONAL MEDICAL HISTORY</b>					
Does <b>the participant's</b> history include any of the following?					
	Yes	No		Yes	No
1 Headaches (Migraine, Sinus)			21 Joint Pain, Arthritis		
2 Allergy, Asthma, or Hay fever			22 Back or Neck Problems		
3 Head Injury, Unconsciousness			23 Swelling of Feet or Hands		
4 Fainting or Dizzy Spells			24 Insomnia		
5 Seizures or Convulsions			25 Mental Illness		
6 Skin Diseases or Rashes			26 Panic Attacks, Depression		
7 Frequent Cold or Bronchitis			27 Sugar, Protein, or Blood in Urine		
8 Lung Disease			28 Diabetes		
9 Shortness of Breath			29 Kidney or Bladder Problems		
10 Heart Condition			30 (Females) Childbirth in last 12 months		
11 Heart Murmur			31 Operations/Surgeries		
12 Irregular Heart Rhythm			32 Illness Requiring Hospitalization		
13 Hypertension			33 Alcohol or Drug Addiction		
14 Chest Pain or Angina			34 Medical Care in the Last Year		
15 Frequent Heartburn or Peptic Ulcers			35 Allergy to Medications, Latex, Food		
16 Stomach or Intestinal Problems, or IBS			36 Weakness or Fatigue		
17 Hepatitis, Jaundice, Liver Problems			37 Lymph Node Swelling or Anemia		
18 Cancer or Tumors			38 Recent Gain or Loss in Weight		
19 HIV/AIDS			39 Oral Lesions or Mouth Sores		
20 Bleeding disorder, hemophilia			40 Other Health Concerns		

MEDICAL CONDITIONS:

Medical Condition	Date of Onset	End Date	Con Med? (Y/N)	Frequency/Comments

ALLERGIES TO MEDICATIONS, LATEX, OR FOOD:

Medication / Latex / Food	Date of Onset	Reaction



**RJRT Clinical Studies Division**  
**Study CSD0914**

**Participant #** \_\_\_\_\_  
**Participant ID** \_\_\_\_\_  
**Date** \_\_\_\_\_

**HOSPITALIZATIONS OR SURGERIES:**

Hospitalization or Surgery	Date

**OTHER COMMENTS:**

---

---

---

---

---

---

**PARTICIPANT AFFIRMATION:**

I certify that to the best of my knowledge the information provided is true and accurate and that I have disclosed all pertinent medical history.

I understand that this information is for confidential research use only and will not be shared with or released to unauthorized persons without my knowledge or consent.

**PARTICIPANT NAME: (Print)** \_\_\_\_\_

**PARTICIPANT SIGNATURE:** \_\_\_\_\_ **DATE:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**REVIEWED WITH PARTICIPANT BY:** \_\_\_\_\_ **DATE:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**MEDICAL ADVISOR SIGNATURE:** \_\_\_\_\_ **DATE:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

UPDATES TO MEDICAL HISTORY:

Reason	Date	Medical Advisor Initials	Participant Initials	Staff Initials

**RJRT Clinical Studies Division**  
**Study CSD0914**

Participant # \_\_\_\_\_

Participant ID \_\_\_\_\_

Date \_\_\_\_\_

**CONCOMITANT MEDICATIONS:**[illegible]

**Product Use Instructions:**

Camel Orbs

Participants will be asked to use one Orb to completion by placing the Orb between their cheek and gum and occasionally moving to a different location in the mouth during use.

Camel Strips

Participants will be asked to use one Strip to completion by placing the Strip on the top of the tongue/roof of mouth or by folding and placing between the lip and gum.

Camel Sticks

Participants will be asked to use ½ of a Stick to completion by placing the Stick portion between their cheek and gum and occasionally moving to a different location in the mouth during use.

Camel Snus

Participants will be asked to place one pouch between either upper or lower lip and gum and to leave in place for a minimum of 15 and a maximum of 30 minutes. Occasional movement of the pouch will be suggested, but not required.

Additional instructions for all products:

You will not be permitted to spit during or after product use in the lab setting.

You will not be permitted to eat or drink while using product in the lab setting.

**The Fagerström Test – Cigarettes**

1. How soon after you wake up do you smoke your first cigarette?

Within 5 minutes ..... \_\_\_\_\_ (3)  
 6 - 30 minutes ..... \_\_\_\_\_ (2)  
 31- 60 minutes ..... \_\_\_\_\_ (1)  
 After 60 minutes ..... \_\_\_\_\_ (0)

2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc.?

Yes ..... \_\_\_\_\_ (1)  
 No ..... \_\_\_\_\_ (0)

3. Which cigarette would you hate most to give up?

The first one in the morning ..... \_\_\_\_\_ (1)  
 Any other.. ..... \_\_\_\_\_ (0)

4. How many cigarettes per day do you smoke?

≤ 10. .... \_\_\_\_\_ (0)  
 11-20 ..... \_\_\_\_\_ (1)  
 21-30 ..... \_\_\_\_\_ (2)  
 ≥ 31. .... \_\_\_\_\_ (3)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

Yes ..... \_\_\_\_\_ (1)  
 No ..... \_\_\_\_\_ (0)

6. Do you smoke if you are so ill that you are in bed most of the day?

Yes ..... \_\_\_\_\_ (1)  
 No ..... \_\_\_\_\_ (0)

Reproduced with permission.

Source: Heatherton, T. F., L. T. Kozlowski, et al. (1991). "The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire." Br J Addict **86**(9): 1119-27

## Mood and Physical Symptoms Scale

Please show for each of the items below how you currently feel.

*(Circle one number for each item.)*

	Not at all	Slightly	Somewhat	Very	Extremely
1. Depressed	1	2	3	4	5
2. Anxious	1	2	3	4	5
3. Irritable	1	2	3	4	5
4. Restless	1	2	3	4	5
5. Hungry	1	2	3	4	5
6. Poor concentration	1	2	3	4	5

7. How strong is your current urge to smoke? *(Circle one number.)*

No urges	Slight	Moderate	Strong	Very strong	Extremely strong
0	1	2	3	4	5

## **DAILY LOG SHEET – Week 1**

**PLEASE RECORD THE NUMBER OF CIGARETTES YOU SMOKE PER DAY  
FOR THE NEXT SEVEN DAYS.**

**\*\*Remember, you are allowed to smoke ONLY your Usual Brand  
cigarettes until the completion of this study.\*\***

<b>Day 1</b>	Number of <b>cigarettes</b> smoked today _____
<b>Day 2</b>	Number of <b>cigarettes</b> smoked today _____
<b>Day 3</b>	Number of <b>cigarettes</b> smoked today _____
<b>Day 4</b>	Number of <b>cigarettes</b> smoked today _____
<b>Day 5</b>	Number of <b>cigarettes</b> smoked today _____
<b>Day 6</b>	Number of <b>cigarettes</b> smoked today _____
<b>Day 7</b>	Number of <b>cigarettes</b> smoked today _____
	<b>* Do <u>NOT</u> smoke after 8:30 p.m. on Day 7.</b>
	<b>Time last smoked on Day 7: _____:</b>

**Comments/Observations concerning the cigarette:**

---

---

---

---

---

---

---

**(Staff only) Reviewed By: \_\_\_\_\_ Date: \_\_\_\_\_**

## **DAILY LOG SHEET – Week 2**

PLEASE RECORD THE NUMBER OF **TOBACCO PRODUCTS** YOU USE PER DAY  
FOR THE NEXT **SEVEN** DAYS.

**\*\*Remember, you are allowed to smoke ONLY your Usual Brand  
cigarettes until the completion of this study.\*\***

Day 1    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

Day 2    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

Day 3    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

Day 4    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

Day 5    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

Day 6    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

Day 7    **Do NOT use oral tobacco products today.**    Number of **cigarettes** smoked today \_\_\_\_\_

**\* Do NOT smoke after 8:30 p.m. on Day 7.**

**Time last smoked on Day 7: \_\_\_\_\_:**

**Comments/Observations concerning the oral tobacco products:**

---

---

---

---

---

---

---

**(Staff only) Reviewed By: \_\_\_\_\_ Date: \_\_\_\_\_**



### **DAILY LOG SHEET – Week 3**

**PLEASE RECORD THE NUMBER OF **TOBACCO PRODUCTS** YOU USE PER DAY  
FOR THE NEXT **SEVEN** DAYS.**

**\*\*Remember, you are allowed to smoke ONLY your Usual Brand  
cigarettes until the completion of this study.\*\***

**Day 1**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 2**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 3**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 4**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 5**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 6**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 7**    **Do NOT use oral tobacco products today.**    Number of **cigarettes** smoked today \_\_\_\_\_

**\* Do NOT smoke after 8:30 p.m. on Day 7.**

**Time last smoked on Day 7: \_\_\_\_\_:\_\_\_\_\_**

**Comments/Observations concerning the oral tobacco products:**

---

---

---

---

---

---

---

**(Staff only) Reviewed By: \_\_\_\_\_ Date: \_\_\_\_\_**

## **DAILY LOG SHEET – Week 4**

**PLEASE RECORD THE NUMBER OF **TOBACCO PRODUCTS** YOU USE PER DAY  
FOR THE NEXT **SEVEN** DAYS.**

**\*\*Remember, you are allowed to smoke ONLY your Usual Brand  
cigarettes until the completion of this study.\*\***

**Day 1**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 2**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 3**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 4**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 5**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 6**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 7**    **Do NOT use oral tobacco products today.**    Number of **cigarettes** smoked today \_\_\_\_\_

**\* Do NOT smoke after 8:30 p.m. on Day 7.**

**Time last smoked on Day 7: \_\_\_\_\_:\_\_\_\_\_**

**Comments/Observations concerning the oral tobacco products:**

---

---

---

---

---

---

---

---

**(Staff only) Reviewed By: \_\_\_\_\_ Date: \_\_\_\_\_**

## **DAILY LOG SHEET – Week 5**

**PLEASE RECORD THE NUMBER OF **TOBACCO PRODUCTS** YOU USE PER DAY  
FOR THE NEXT **SEVEN** DAYS.**

**\*\*Remember, you are allowed to smoke ONLY your Usual Brand  
cigarettes until the completion of this study.\*\***

**Day 1**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 2**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 3**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 4**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 5**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 6**    No. of **oral tobacco products** used today \_\_\_\_\_    Number of **cigarettes** smoked today \_\_\_\_\_

**Day 7**    **Do NOT use oral tobacco products today.**    Number of **cigarettes** smoked today \_\_\_\_\_

**\* Do NOT smoke after 8:30 p.m. on Day 7.**

**Time last smoked on Day 7: \_\_\_\_\_:\_\_\_\_\_**

**Comments/Observations concerning the oral tobacco products:**

---

---

---

---

---

---

---

**(Staff only) Reviewed By: \_\_\_\_\_ Date: \_\_\_\_\_**