UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Summary of Changes between Generations of Protocol SCI-001

FROM: John M. Carley
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TO: Paul Lewis
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As you know, we have in hand (and have provided to the members of the HSRB) three different versions of the insect repellent efficacy test protocol SCI-001, scheduled for discussion at the Board's meeting later this month. These three generations of the protocol are dated November 2, 2006, December 14, 2006, and December 29, 2006. Only the first and third versions included an Informed Consent Form (ICF); the ICF associated with the first generation of the protocol was approved by the IRB on November 7, 2006. The revised ICF associated with the third generation of the protocol was approved by the IRB on January 2, 2007.

I have gone through all three documents carefully, and I've listed below what changed from each generation to the next, using redline/strike-out conventions. In general, the changes clarify passages that were originally confusing, or clarify that the "experienced personnel" who serve as untreated controls are subjects, too. A few changes correct frank errors; a few frank errors remain to be corrected.

Although I may have missed some small changes, I believe the summary below is essentially complete. Please share it with the Board members, to make their preparation for the meeting a little easier.

I. Protocol SCI-001 changes from v.1 (November 2, 2006) to v.2 (December 14, 2006):

- p. 3 of 46: Objective restated in §5.1. "The objectives of this study ~~is~~ are to test the mosquito repellent efficacy characteristics of the Test Materials, compare them to one another, and contrast the [sic] with a comparison article that is the US Military issue topical insect repellent. Note that ~~against mosquitoes, with~~ efficacy will be measured as Complete Protection Time."

- pp. 3-4 of 46: Description of main endpoint revised, §5.2, ¶3: ". . . The efficacy study will consist of two field trials. In each trial, each formulation, including the comparison article, will be tested by ten subjects, with ~~, with 10 treated subjects in each trial testing each formulation, and~~ two untreated subjects. ~~in each trial. In addition, the current US Military repellent (the DEET-based 'Ultrathon') will be used a comparison article.~~ Initial dosage determination ('dosimetry') will be conducted with 10 subjects per formulation, some of whom may go on to participate in efficacy testing. . . . When 10 subjects have completed dosimetry for each formulation, including the comparison article, those data will be used to determine dosing for the efficacy testing."

- p. 5 of 46, ¶3: "In each trail [sic] only two experienced, qualified subjects ~~professionals (the Study Director and/or other qualified researchers)~~ will expose untreated limbs to monitor biting pressure, . . ."

- p. 6 of 46, end of ¶2: New sentence added: "In addition, the US Military is seeking improved DEET formulations, and is limited in its consideration to EPA-registered products."

- p. 9 of 46, §6.2.1: "The negative control is untreated ~~for both dosimetry and~~ in the repellency assays."

- p. 12 of 46, §8.1, last 3 lines: "The dosimetry study is an examination of dosing behavior. Hence, for ~~In~~ dosimetry ~~testing~~, all subjects are treated, and there is not an untreated control group."

- p. 13 of 46, §8.3.1. New text added at end of subsection: "To be regarded as experienced personnel, a candidate subject must have an undergraduate (or higher) degree in life sciences, of [sic] be a vector control professional, or have participated in at least 5 Carroll-Loye repellent efficacy studies. In addition, that person must meet all of the other participation criteria listed in §§9.1.1.1 and 9.1.1.2."

- p. 14 of 46, §8.3.2. Lines 37-40 added to treatment allocation table.

- p. 16 of 46, §9.1.3, ¶ 1: "In efficacy testing, we will use 10 subjects per treatment and 2 untreated control subjects per field trial. ~~in efficacy testing~~. Each subject is a replicate. In the dosimetry portion of the study, 10 subjects will be engaged to apply each repellent, including the comparison article. ~~For the Comparison Article, we propose to initially test six subjects, with the possibility of enrolling up to 10 if initial analyses indicate that greater statistical power would assist in resolving important ambiguities."~~

- p. 26 of 46, §10.3.4, last ¶: "After you have completed an application successfully, the technician will instruct you to wash and dry the treated arm . . . . You will continue until you have completed three successful applications to the arm. Then you will repeat the entire procedure above, but with a lower leg. You will complete this sequence of three

arm applications, and three leg applications for each of the repellents being studied. For each repellent you will begin with a practice application to familiarize yourself with how it comes out of the tube, and how it covers and spreads on the skin.""

- p. 30 of 46, §11.2: "For dosimetry, there will be 10 treated subjects testing each of the three repellent formulations and the ~~positive control~~ comparison article. For ~~repellency~~ efficacy testing, there will be 10 subjects treated with each test ~~repellent~~ material and two serving as untreated controls ~~for repellency testing~~ at each of two sites."

- p. 37 of 46: New form for recording limb measurements of subjects

- p. 38 of 46: Revised form for recording dosimetry phase

- p. 39 of 46: Revised form for recording efficacy phase

- pp. 40-44 of 46: New appendix containing instructions to subjects for dosimetry phase (pp. 41-43) and for use of mechanical aspirators (p. 44).

- p. 45 of 46: Revised ICF not included in v.2.

- MSDS's for all materials removed from protocol v.2 to separate document

II. Protocol SCI-001 changes from v.2 (December 14, 2006) to v.3 (December 29, 2006):

- p. 5 of 56: ¶ 3, lines 7-9: In each trail, [sic] only two experienced, qualified subjects (qualification criteria described in §9.1) will expose untreated limbs . . ."

- p. 9 of 56: Text of §6.2.1 "The negative control is untreated ~~in the~~ for both dosimetry and repellency assays." *[Note that this is a return to v.1]*

- p. 11 of 56: Text in §6.4 "Mosquito specimens will be collected from untreated control subjects, and from the protective clothing of all subjects, during testing. . "

- p. 15 of 56: §9.1.1 title: "Inclusion criteria, all subjects:"
  §9.1.2 entire subsection is new
  §9.1.3 title: "Exclusion criteria, all subjects:"

- pp. 15-21 of 56: All subsections §§9.1.2 – 9.1.6 re-designated as §§9.1.3 – 9.1.7

- p. 19 of 56: end of paragraph i): ". . . Those who will serve as untreated control subjects are limited to experienced technical personnel, who are screened with the same exclusion criteria as are other subjects, and have additional inclusion requirement."

- p. 32 of 56: §11.3.2, last ¶, third sentence: "Ambient LIBing pressure as measured by ~~the technical personnel serving as~~ untreated subjects will be presented tabulated [sic] by individual and exposure period."

- pp. 46-55 of 56: New IIRB approval letter and ICF

III. ICF changes from v.1 (version 11/7/06) to v.3 (version 1/2/07)

- ICF p. 1 of 9, "Nature and Purpose", ¶ 2: "The purpose of the study is to test how well new lotion insect repellent products work outdoors against mosquitoes. These ~~three~~ four products, which are similar to some already being sold, have been formulated to be more cosmetically acceptable to users. The information gained from the study will assist in the development of these repellents for future commercial marketing. During the study we will first measure how much insect repellent ~~you~~ subjects put on ~~your~~ their own arms and legs in a visit to the study laboratory~~, and train you to use a mechanical mosquito catcher~~. On a later date, we will go to a field site to test the insect repellents against mosquitoes in nature. You may be asked to participate in one or both parts of the study."

- ICF p. 2 of 9, "Study Introduction and Duration", Visit 1 ¶ 1: "Within 21 days before the field study visit you will ~~go to the laboratory and~~ meet with a researcher . . . ."

- ICF p. 3 of 9, "Study Introduction and Duration", Visit 2, New ¶ 2: "The Principal Investigator may also ask if you would like to participate in a second field test of these products, using the same procedures as in the first test, on a later date. You may refuse to participate in additional testing without penalty to your compensation."

- ICF p. 3 of 9, "Study Procedures: Study Design" ¶ 1 "The study will test ~~three~~ four different insect repellent ~~products, namely a lotion, a pump spray and an aerosol spray~~ lotions. You will be randomly (by chance) assigned to receive one ~~or two of the three~~ product~~s~~, so your chance of receiving any one ~~of them~~ product is one-in-four ~~one-in-three or two-in-three~~. You will not have a choice as to which repellent product ~~or products~~ you receive. If you participate on more than one day, you will receive a different product on different days. For each product assigned to you, you will have an amount typical of what people commonly use applied to your forearms or lower legs. Two experienced ~~personnel~~ subjects will also ~~be present~~ participate to record the activity of mosquitoes by exposing their own arms or legs without repellent applied. Experienced subjects are pre-qualified by the Principal Investigator, and designated before the field test begins. Unless you have been qualified in advance as an experienced subject and agreed to expose untreated skin, ~~However,~~ you will not be asked to expose untreated skin and should avoid doing so."

- ICF pp. 3-4 of 9, "Study Procedures: Procedures: Visit 1": At the laboratory, a researcher will measure the length and circumference of your forearm and lower leg. If you are participating in this part of the study, you will then practice using the products to

decide how you best like to apply them and how much you would apply to your forearm or lower leg in order to have thorough and even coverage. The researcher will answer any questions you have about the application. Once you have a method you are satisfied with, you will wash your arms and lower legs with soap and water and dry them with a towel. The researcher will then ~~place three small "bracelets" made of medical gauze around your arm or leg. You will then spray that area, including the bracelets, with a repellent, and a technician will remove the gauze and weigh it to determine how much spray has clung to its surface. Similarly, we will~~ ask you to apply an amount of the lotion repellent product to your skin that you think gives complete and even coverage. We will use the amounts you apply in this part of the study to determine how much repellent people normally apply.

- ICF p. 5 of 9, "Study Procedures: Procedures: Visit 2" new final paragraph added: "If you are one of the two untreated ("experienced") subjects, two technicians with aspirators will assist you in watching for and removing mosquitoes during each one-minute exposure, and in each exposure you should cover your limb with the protective fabric as soon as the first mosquito lands and attempts to bite, and keep it covered until the next exposure period, 15 minutes later."

- ICF p. 6 of 9, "Risks/Discomforts", ¶ 2: "~~The spray repellents contain alcohol and are flammable.~~ There is a small possibility . . . ."