Compilation of E-mail exchanged between Scott P. Carroll of Carroll-Loye Biological Research and John M. Carley of EPA concerning Repellent Protocol SCI-001 from November 8, 2006 through December 14, 2006. The correspondence reads from the bottom up.

From Scott P Carroll <spcarroll@ucdavis.edu> 12/14/2006 04:50 PM

To John Carley/DC/USEPA/US@EPA
cc
bcc
Subject Revision: Repellent protocol SCI-001

Dear John,

I have revised our protocol SCI-001 for consideration by the HSRB.

The main changes are as follows.

The objective of comparing efficacy of the other deet materials to Ultrathon has been elevated and justified.

The notion of a positive control (Ultrathon) has been eliminated in favor of consistently regarding Ultrathon as the comparison article.

The number of subjects in each test and the number of materials per subject are now unambiguously specified for all materials (always 10).

It is now specified that the comparison article will undergo dosimetry testing in the same manner as the other materials.

The Study Director has been eliminated as a negative control. The qualifications of negative controls have been specified in the protocol.

Via discussion with personnel at IIRB we will determine how best to revise the ICF for both treated and untreated (control) subjects. The revised, approved ICF will be submitted as soon as possible, most likely this month.

Data collecting forms have been improved/added

The MSDS/Label docs have been shifted to a separate file that is noted in the Protocol ToC (pg 1).

The errors of reference to another sponsor and to a spray formulation have been corrected in the ICF.

Carroll SCI-001 Support Docs.pdf

I need to send this too you now.

Thanks for your review.

Best Regards,
Scott

From John Carley/DC/USEPA/US@EPA 12/10/2006 11:03 AM

To Scott P Carroll <spcarroll@ucdavis.edu>
Cc
Bcc
Subject RE: Repellent protocol SCI-001 review

First, it seems to me that whether you use one or two ICFs you'll need to say something back in the discussion of recruiting/informing about how you will identify candidates to be the "experienced subjects", what you will tell them that's different from what all subjects are told, and how you'll select them.

Then there needs either to be a separate ICF for the untreated controls or you'll have to split a single ICF into multiple tracks. The latter approach could make the ICF confusing for most of the subjects, and possibly also for the IRB, for EPA, or for the HSRB. Without having worked my way through the ICF to see how often and exactly where it would need to be split, I'm not sure how feasible the multi- track approach would be. If it can be done without making an already bulky ICF a lot bulkier and harder to follow, I see no objection. But I think two separate ICFs might actually be easier to get right.

On another note, late Friday we got the "final draft report" of the October HSRB meeting. The Board will discuss final changes in a publicly accessible telephone conference on Thursday January 18 from 1-4:00 PM Eastern time. I see no surprises in the discussion of your protocols.

John M. Carley
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From Scott P Carroll <spcarroll@ucdavis.edu> 12/08/2006 06:49 PM

To John Carley/DC/USEPA/US@EPA
cc
bcc
Subject RE: Repellent protocol SCI-001

You make a valid point regarding the untreated controls. Perhaps that point was not fully addressed in the EMD mosquito tests. I wonder if it would be pertinent to revise the ICF in order to accommodate both classes of individuals, defining those 'experienced subjects' on the basis of background. That seems more straightforward that having multiple ICFs. I'd appreciate your opinion on the matter.

Scott

From Scott P Carroll <spcarroll@ucdavis.edu> 12/08/2006 04:15 PM

To John Carley/DC/USEPA/US@EPA
cc
bcc
Subject RE: Repellent protocol SCI-001

HI John,

I have examined your detailed review. I will proceed according to your suggestions, aiming for a re-submission by next Friday.

Thanks very much, best for the weekend, and for any holiday preparations before you.

Scott

From John Carley/DC/USEPA/US@EPA 12/8/2006 04:39 PM

To Scott P Carroll <spcarroll@ucdavis.edu>
Cc
Bcc
Subject RE: Repellent protocol SCI-001 review

I wish it were otherwise, but I've not yet received anything from the science reviewer working on SCI-001, so there may be more comments still. I'll let you know as soon as I can if he has any concerns.

I did notice one more potential problem. The ICF clearly applies only to treated subjects: "Experienced personnel will also be present to record the activity of mosquitoes by exposing their own arms or legs without repellent applied. However, you will not be asked to expose untreated skin and should avoid doing so." (p. 36)

The untreated controls are also subjects in the research, and must also be informed, and must consent to participate. It looks to me like you need another ICF for the untreated controls. And, given the HSRB discussion of the repellent guidelines in their June meeting, if you are planning to be one of the untreated controls (see ref. at the top of p. 5) you need to take special pains to demonstrate the consistency of your participation in the research as a subject with your role as Principal Investigator.

Am I missing something?

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From John Carley/DC/USEPA/US@EPA 12/8/2006 01:17 PM

To Scott P Carroll <spcarroll@ucdavis.edu>
Cc
Bcc
Subject RE: Repellent protocol SCI-001 review

Sorry this has taken me so long. If you can resubmit protocol SCI-001 by next Friday, we'll have time to reflect the revisions in our reviews, which must be released by 12/20.

I have noted the following points in protocol SCI-001 requiring clarification or supplementation:

The discussion of the dosimetry phase is sketchy and confusing—in part because it is scattered throughout the protocol. It would be better to isolate it in a separate section of the protocol.

Multiple references to the numbers of subjects are confusing (pp. 3 "10 subjects", p. 10 "all subjects", p. 13 "10 subjects", p. 25 "For dosimetry there will be 10 treated subjects testing each of the three repellent formulations and the positive control.") The ICF suggests that all subjects will participate in the dosimetry phase (p. 34.) If fewer than all subjects will be involved in dosimetry, it is not clear how subjects for the dosimetry phase will be selected.

The discussion on p. 21 is unclear about whether each subject is to apply each of the three test materials once to an arm and once to a leg, for a total of three applications to an arm and three to a leg, or whether each subject is to apply each of the three test materials three times to an arm and three times to a leg, for total of nine applications to an arm and nine to a leg. If only a single application of each material is made to each limb of each subject, what is the "subject mean?" It is not clear how the average across dosimetry subjects would be the "mean of means" as it is characterized on pp. 23 and 25.

There is no discussion of dosimetry for the positive control; how will dosage be established for this material?

The documentation of the dosimetry phase could be improved by labeling the recording form (p. 31) and by providing for documenting the calculations of mean dosage rates for use in the repellency phase.

There is also a reference to untreated controls not being treated in the dosimetry phase (p. 8); it should be clarified that there are no controls, treated or untreated, in the dosimetry phase.

A form for recording the dimensions of each subject's forearm(s) and lower leg(s), and for calculating the appropriate dose for the repellency phase, should be added.

As I mentioned in an earlier note, the training materials on use of aspirators should be included as an appendix to the protocol.

The number of treatments per subject is unclear. The ICF (p. 36) suggests that subjects may receive "one or two of the three products". On page 23 the protocol states that a technician will apply repellent to subjects' "forearms or lower legs"--ambiguously plural in both cases. But the dosing scheme presented on pp. 11-12 indicates only a single treatment per subject, consistent with the ICF statement (p. 35) that "about 40 volunteers will be enrolled."

The number of subjects receiving the positive control material should be defined unambiguously. The protocol states (p. 13) that this number will be at least 6 but perhaps as many as 10, based on the results of unspecified "initial analyses." It would be appropriate to do these analyses, and reflect them in a protocol that clearly states how many subjects will receive this material. The use of the positive control data in statistical analysis should also be specified.

I have also noted two frank errors requiring correction, both in the ICF:

The second paragraph on p. 39, beginning with the words "The spray repellents contain alcohol . . . " is irrelevant to all test materials, none of which are sprays or contain alcohol. This paragraph must be deleted and replaced with one characterizing the potential risks associated with the test and positive control materials in their lotion form.

On p. 41 the sponsor is identified incorrectly as EMD Chemicals, Inc.

Although the correspondence is now scattered across several documents, I won't ask you to recompile it unless there is more I don't know about.

For your information, here is my completeness checklist for this protocol. If you think I've missed something or erred, please let me know ASAP.

John M. Carley
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From Scott P Carroll<spcarroll@ucdavis.edu> 11/17/2006 01:42 AM
To John Carley/DC/USEPA/US@EPA
cc
Subject RE: Repellent protocol SCI-001 review

Hi John,

Let's start with the ICF date. I submitted the protocol with ICF on 11/3 as the correspondence indicates. IIRB added the text of the CA study subject's bill of rights as the final page, and used their approval date as the nominal date for that document. There was no intermediate exchange of correspondence regarding that change, and no discussion of the date. It seemed straightforward to me.

Re the EMD reference standing erect in the ICF; sadly I can still search for that black term in the documents and Adobe does not detect the remaining miscreant in the least. Hopefully there is something to the affect of a 'Carley enhancement' that I download as shareware or order on line.

To make that change I have asked to IRB to consider an expedited administrative change.

In addition, not including the training documents was an oversight as we will continue to employ them; if you are indeed comfortable with my still including them I will do so next week when I submit the protocol with the corrected ICF.

Lastly, I will attach the protocol's IIRB 'site questionnaire' here.


Site_Questionnaire_SCI-001.doc

Please let me know if there remain items that you would like me to address.

Many thanks for your review.

Scott

From John Carley/DC/USEPA/US@EPA 11/15/2006 04:32 PM

To Scott P Carroll <spcarroll@ucdavis.edu>
Cc
Bcc
Subject RE: Repellent protocol SCI-001 review

In addition to the missing IRB materials I mentioned in the email I copied to IIRB, I have some other quick comments:

I noted the absence of the subject training materials (on dosimetry testing and use of the aspirator) you included in the similar protocol EMD-004 we reviewed earlier. I think these were important to the HSRB, and that it would be prudent to incorporate them again.

There is an erroneous reference to EMD as the sponsor in the confidentiality discussion on page 41

I'm confused by the date of the approved ICF. It's dated 11/7/06, yet the correspondence indicates that you submitted the package to IIRB on 11/3. Was there an intermediate exchange concerning an earlier draft of the ICF leading to a revision on 11/7? If so, please document that exchange. If not, please explain the date discrepancy.

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From John Carley/DC/USEPA/US@EPA 11/15/2006 04:14 PM

To Scott P Carroll <spcarroll@ucdavis.edu>
Cc Robert Roogow <rroogow@iirb.com>
Bcc
Subject RE: Repellent protocol SCI-001 review

I have not yet received either the IRB minutes or the documentation of IRB membership as required by 40 CFR 26.1125 and as specified by 40 CFR 26.1115(a)(2) and (5). These are needed to complete the protocol package before it can enter review.

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From Scott P Carroll<spcarroll@ucdavis.edu> 11/08/2006 05:03 PM
To John Carley/DC/USEPA/US@EPA
cc
Subject Submission of Mosq Repellent Protocol SCI-001 for HSRB consideration

Dear John,

Thanks for your help today. With this email I submit a mosquito repellent protocol similar to those considered in the foregoing HSRB meetings, but with different actives and a different sponsor.

My correspondence with the IRB regarding the review of the protocol is also attached.

Notification of IRB approval is in the IRB documents appended to the protocol.

Please let me know if you have additional questions regarding these materials.

Sincerely,
Scott

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