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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 26, 2007

MEMORANDUM

SUBJECT: Ethics Review of Reports of Completed Carroll-Loye Field Efficacy Studies SCI-001 and WPC-001 for Mosquito Repellents

FROM: John M. Carley
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TO: Marion Johnson, Chief
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REF: Carroll, S. (2007) Test of Dermaegis LipoDEET 302 Personal Insect Repellent: EPA Reg. #82810-1. Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.1. 219 p. (MRID 47211901)

Carroll, S. (2007) Test of Dermaegis LipoDEET 3434 Personal Insect Repellent. Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.2. 222 p. (MRID 47208401)

Carroll, S. (2007) Test of Coulston's Duranon Personal Insect Repellent (EPA Reg. #50404-8). Unpublished study prepared by Carroll-Loye Biological Research under Project No. SCI-001.3. 217 p. (MRID 47211801)

Carroll, S. (2007) Test of an Oil Of Lemon Eucalyptus-Based Personal Insect Repellent: EPA Reg. #305-62. Unpublished study prepared by Carroll-Loye Biological Research under Project No. WPC-001. 225 p. (MRID 47217601)

I have reviewed all available information concerning the ethical conduct of the research

reported in the referenced documents, which describe the concurrently executed Carroll-Loye protocols SCI-001 and WPC-001. Both are field tests of the efficacy of mosquito repellents.

Background

I have reviewed the reports of SCI-001 and WPC-001 together because the protocols are very similar, and because they were executed concurrently in the field. Many of the treated subjects participated in both studies; both studies relied on the same untreated controls at each site on each day of field testing. Although there are some important distinctions to be made between the two studies, their conduct cannot be adequately understood if they are treated separately.

It is even more important to review the three separately submitted reports of SCI-001 as a single study. This protocol called for comparing the performance of each of three test repellents to the U.S. military standard repellent. It was executed only once, but the results were reported separately for each of the three test repellents. Most of the 200+ pages in each of the three reports duplicate pages in the other two reports. I have highlighted in this memorandum where the information unique to each sub-study can be found.

The principal differences between the protocols are (1) whereas the same consent document served for both treated and untreated subjects in SCI-001, separate consent documents for treated and untreated subjects were used in WPC-001; (2) whereas SCI-001 tested four repellents, WPC-001 tested only one; and (3) whereas SCI-001 was not amended to better explain recruitment of "experienced subjects" to serve as untreated control, WPC-001 was.

Scope of Review:

SCI-001

This review reflects consideration of the three separate sub-study reports cited above, and the following additional documents:

- EPA's protocol review of December 20, 2006
- The HSRB's April 16 report of its January 2007 discussion of SCI-001
- Carroll-Loye Biological Research's September 24, 2007 response to EPA's request for additional information about LipoDEET-3434 and the rationale for the amendment by which it became one of the test repellents

WPC-001

This review reflects consideration of the study report cited above, and the following additional documents:

- EPA's protocol review of March 13, 2007
- The HSRB's June 13 report of its April 2007 discussion of WPC-001

- Carroll-Loye Biological Research's September 20, 2007 response to EPA's request for additional information concerning which subjects signed which version(s) of the consent document on what date(s)

Completeness of Submission: SCI-001

As noted above, much of the content of the three submitted sub-study reports is duplicative. The submitter has highlighted the passages in the body of the reports of sub-studies SCI-001.2 and SCI-001.3 which differ from SCI-001.1. Table 1 below shows how the content of the appendices of the three reports differ.

Table 1
Content of Appendices to Study Reports SCI-001.1, -001.2, and -001.3
Material unique to a single report is highlighted in color

App No.	Content of Appendix	Page Range in Each Volume of Report		
		MRID 47211901 SCI-001.1 LipoDEET 302	MRID 47208401 SCI-001.2 LipoDEET 3434	MRID 47211801 SCI-001.3 Duranon
1	Efficacy Data Spreadsheets	19-22	20-23	20-23
2	Efficacy Data Capture Forms	23-35	24-36	24-36
3	Subject Treatment and Dosing	36-37	37-38	37-38
4	Environmental Conditions	38-44	39-45	39-45
5	Dosimetry Data Spreadsheet	45-46	46-47	46-47
6	Subject Limb Measurements[1]	47-77	48-80	48-76
7	Dosimetry Data Capture Forms	78-98	81-101	77-97
8	Approved protocol and consent forms			
	• 12/29/06 protocol	99-134	103-137	99-133
	• Data recording forms	135-138	138-141	134-137
	• Subject training documents	139-143	142-146	138-142
	• 1/2/07 IRB Approval Letter	144-145	147-148	143-144
	• 1/2/07 Approved CD & CDPR Bill of Rights	146-155	149-158	145-154
	• 1/22/07 IRB Correction Letter	156	159	155
	• 1/22/07 Corrected CD & CDPR Bill of Rights[2]	157-174	160-177	156-173
	• Label & MSDS for Insect-Guard II[3]	175-179	178-182	174-178
	• Label & MSDS for Coulston's Duranon	180-187	183-190	179-186
	• Label & MSDS for LipoDEET 302	188-196	191-199	187-195
	• Label & MSDS for 3M Ultrathon	197-208	200-211	196-207
	• Amendment to change test material	n/a	212	n/a
	• Amendment to add virus assay	209	213	208
	• Deviations from protocol	210-211	214-215	209-210
9	Mosquito ID and Viral Assay	212-215	216-219	211-214
10	Physical plan of Carroll-Loye Laboratory	216-217	220	215
11	Additional Correspondence C-L:IIRB 1/22/07	218-219	221-222	216-217

[1] Although there are slight differences, this material is largely the same across the three study reports. Measurements for subjects 22, 25, and 62 are reported only in SCI-001.1; for subjects 28, 32, 43, and 70 only in SCI-001.2, and for subjects 10 and 69 only in SCI-001.3

[2] The cited page range in each report includes two duplicate copies of the 1/22/07 corrected consent document

[3] This material describes the test repellent deleted from testing by amendment of 2 July 07

All three submitted sub-study reports contain an apparently complete record of correspondence between the investigators and the IIRB after the January HSRB meeting. In response to a request from EPA on September 18, Carroll-Loye Biological Research submitted a completed EPA "Confidential Statement of Formula" form and an MSDS describing LipoDEET 3434. Both documents were dated September 24, 2007. The checklist used by EPA to verify satisfaction of the requirements of §26.1303 as they apply to the reports of SCI-001 appears as Attachment 1 to this memorandum.

Completeness of Submission: WPC-001

The study report as submitted contains an apparently complete record of correspondence between the investigators and the IIRB after the April HSRB meeting. In response to a request from EPA on September 13, Carroll-Loye Biological Research submitted to EPA on September 20 a clarification of which subjects had signed which versions of the consent document on what date(s). The checklist used by EPA to verify satisfaction of the requirements of §26.1303 as they apply to the report of WPC-001 appears as Attachment 2 to this memorandum.

Table 2
Content of Appendices: WPC-001

App No.	Content of Appendix	Page range
1	Efficacy data spreadsheet	20-21
2	Efficacy data capture worksheets	22-25
3	Calculation of individual subject doses	26-29
4	Environmental measures	30-33
5	Deviations from protocol	34-35
6	Plan of Carroll-Loye laboratory	36
7	Protocol, amendments, and approved revisions to consent documents • 16 Jan 07 Protocol • 14 Jun 07 Amendments • 19 Jun 07 IIRB approval of amendments and revised CDs • 19 Jun 07 Approved CD – treated subjects • 19 Jun 07 Approved CD – untreated subjects • 10 Jul 07 IIRB Approval of further revised CDs • 10 Jul 07 Approved CD – treated subjects • 10 Jul 07 Approved CD – untreated subjects • 13 Jul 07 IIRB approval of further revised CD for untreated subjects • 13 Jul 07 Approved CD – untreated subjects (pp. 159-167)	37-167 38-112 113-119 120 121-129 130-138 139 140-148 149-157 158 159-167
8	Subject limb dimension forms	168-193
9	Dosimetry data spreadsheet and data capture forms	194-216
10	Certificate of analysis	217
11	Additional IIRB correspondence, including "sponsor letters" cited in IIRB approvals of 10 Jul and 13 Jul	218-222
12	Mosquito ID and virus assay	223-225

Protocol Deviations

The same six deviations from the protocols are reported for both studies, as well as one additional deviation specific to WPC-001. None were considered by the investigator to have affected the integrity of the research or the safety of the subjects. Two, however, may have important implications.

- In both studies "experienced subjects"—presumably those who also served as untreated controls, although this is not made explicit—assisted the investigators to treat the other subjects. It is unclear whether participation in treatment of other subjects was appropriate for these subjects, whatever their level of experience; it certainly wasn't described to them in the consent documents they signed.

- In both studies it is reported that on July 12 subjects failed to maintain the distance between themselves and other subjects specified in the protocol. This is explained with the assertion that *"Because all subjects were wearing the same repellent, any interactions among them with regard to repellent performance that might have been augmented by excessive proximity are unlikely to complicate the interpretation of the results."* Without disputing the likelihood that interactions between subjects might have complicated the interpretation of results, it is beyond dispute that on July 12 all subjects were in fact ***not*** wearing the same repellent, due to the concurrent execution of the two protocols.

Although it was not reported as a deviation from the protocol, subject limb measurement was initiated for WPC-001 before the reported date of "study initiation" or the date on which the subjects were reported to have signed consent documents. Since the same measurements applied when the same subject participated in SCI-001 and WPC-001, and since the initiation of SCI-001 preceded that of WPC-001 by a week, this is only of concern in the case of subject 29, who did not participate in SCI-001, whose limbs were measured on July 7, and who did not sign a consent form until July 11. In his response to EPA of September 24, reporting which subjects signed which versions of the consent documents on which dates, the investigator acknowledges that available records show that subject 60 signed the consent document for WPC-001 on July 12, two days after participating in dosimetry testing for WPC-001.

Also not reported as a deviation from the protocols, because field trials were conducted on consecutive days (July 7-8 and July 12-13-14-15) using many of the same subjects, in many instances a subject's participation on July 8, 13, 14, or 15 violated the exclusion criterion common to both protocols disallowing participation by anyone who had used a repellent "within one day preceding the study." This affected 35 of the 81 efficacy values reported for SCI-001, and 11 of the 20 efficacy values reported for WPC-001.

Calendar of Activities: SCI-001 and WPC-001

Table 3 below arrays key events in the development, review, execution, and reporting of both studies, demonstrating the many interconnections between them.

Table 3
Integrated Timeline of Key Events: SCI-001 and WPC-001 Repellent Studies

SCI-001	Date	WPC-001
EPA Science & Ethics Review of SCI-001	12/20	
Carroll-Loye revises SCI-001 protocol and CD	12/29	
IIRB approves revised protocol and CD	1/2	
	1/16	Carroll-Loye submits protocol and CD for IIRB review
IIRB approves corrected version of 1/2/07 CD	1/22	
	1/23	IIRB approves 16 Jan protocol and (single) CD
HSRB discussion of SCI-001	1/24	
	3/13	EPA Science & Ethics Review of WPC-001
HSRB report of Jan 24 meeting released	4/16	
	4/18	HSRB discussion of WPC-001
	6/13	HSRB report of April 18-20 meeting released
	6/14	C-LBR submits amendments to protocol and revised separate CDs for treated and untreated subjects for IIRB review
	6/19	IIRB approves amendments and revised CDs
Amendments to add viral assay of collected mosquitoes and to change test repellent to LipoDEET-3434	7/2	
"Study Initiation Date"	7/3	
	7/4	C-LBR submits further revised CDs for treated and untreated subjects for IIRB review
Subject limb measurement	7/3-11	
Dosimetry testing	7/3-5	
	7/4-11	Subject limb measurement (Subject 29, measured 7/7, and subjects 17, 36, and 38, measured 7/11, participated only in WPC-001. Other subjects also participated in SCI-001. Only subject 29 was measured before signing CD.)
Field testing in Butte County	7/7	
Field testing in Butte County	7/8	
	7/9	C-LBR explains revisions to CDs in e-mail to IIRB
	7/10	IIRB approves revised CDs for treated and untreated subjects
	7/10	"Study Initiation Date"
	7/10-15	Treated subjects sign CD approved 7/10
	7/10-11	Dosimetry testing (Only subject 60 may have participated on 7/10 before signing CD on 7/12)
	7/11	Untreated subjects sign CD approved 7/10
	7/12	C-LBR submits further revised CD for untreated subjects for IIRB review
Field testing in Glenn County	7/12	Field testing in Glenn County
Field testing in Glenn County	7/13	Field testing in Glenn County
	7/13	IIRB approves further revised CD for untreated subjects
Field testing in Glenn County	7/14	
Field testing in Butte County	7/15	Field testing in Butte County
	7/16	Untreated subjects sign CD approved 7/13
	8/1	"Study completion date"
"Study completion date"	8/2	
	9/13	EPA requests clarification of which subjects signed which CDs, and when
EPA requests additional information about LipoDEET 3434	9/18	
	9/20	C-LBR provides requested clarification
C-LBR provides requested information	9/24	

Analysis by Subject Number

It is not possible to adequately understand the degree to which execution of these two studies was interconnected except by tracking the participation of each subject. Attachment 3 to this memorandum arrays information garnered from all four study reports by subject number, with associated explanatory notes.

Applicable Ethical Standards

Both studies were initiated after April 7, 2006, so prior submission of the protocol and supporting materials to EPA was required by 40 CFR §26.1125. 40 CFR §26.1601(c) required EPA to provide the protocol to the HSRB for review. Suggestions made in EPA and HSRB reviews, and the investigator's response to them, are noted for each protocol below.

EPA and HSRB Comments in Prior Reviews of SCI-001

EPA noted the following ethical deficiencies in its December 20, 2006 review of SCI-001:

- The protocol does not describe how the "experienced" subjects who will serve as untreated controls will be recruited, or how the process of informing them and obtaining their consent to this special role in the research will differ from the process used for the treated subjects.

  No changes were made in the SCI-001 protocol or consent document in response to this comment.

- Risks from exposure to the test materials themselves are mischaracterized in the Informed Consent Form, which refers to test materials intended for spray application and containing alcohol. This passage must be replaced by a description of the risks associated with exposure to the test materials—all of which are lotions not containing alcohol.

  This was corrected in the consent document approved by IIRB on January 2, 2007.

- Either a revised Informed Consent Form covering both the untreated and treated subjects, or a separate form for the untreated controls, must be provided and approved by the IRB.

  Satisfactorily addressed in consent document revised subsequent to EPA review, approved by IIRB January 2, 2007 and corrected by IIRB January 22, 2007.

In its April 16, 2007, final report of the January 24, 2007 meeting, the HSRB stated its concurrence with EPA's finding that if protocol SCI-001 were revised as suggested by EPA and the HSRB it would meet the applicable ethical requirements of 40 CFR 26 subparts K and L. The HSRB report also included the following specific suggestions:

- The investigator should collect mosquitoes during the field studies and subject them to serologic or molecular analysis to confirm absence of known pathogens.

  The protocol was amended on July 2, 2007 to incorporate viral assay of field-collected mosquitoes.

- The protocol should clarify how untreated controls will be recruited.

  Not addressed.

- The informed-consent document (1) mischaracterizes the test materials as containing alcohol; (2) is structured so it doesn't apply to untreated control subjects; and (3) should say "up to 48 (10 exposed and 2 controls per arm of the study)" subjects will participate.

  Point (1) was corrected in the January 2 2007 consent document. Point (2) was addressed by the January 2, 2007 consent document, which applied to both treated and untreated subjects. The consent document has not been changed further since the HSRB's January meeting. The consent document was not changed to address point (3); the actual number of participants was 37-41 subjects. 37 were uniquely identified by number; up to 4 more served as untreated controls on July 8 and 14, but were identified only by function.

- It is difficult to assess qualifications of IIRB; the Board would like to see some evidence of member training, IIRB accreditation, etc.

  No additional information about IIRB member qualifications or IIRB accreditation has been provided.

EPA and HSRB Comments in Prior Reviews of WPC-001

EPA noted the following ethical deficiencies in its March 13, 2007 review of WPC-001:

- Methods proposed for managing information about prospective and enrolled subjects will generally protect their privacy from compromise. Greater assurance could be provided, however, if data collection forms referred to subjects only by coded number rather than by name.

  Forms were changed as requested by amendment #7 of June 14, 2007

- Although additional inclusion factors are defined for the "experienced" subjects who will serve as untreated controls, the protocol does not describe how they will be recruited, or how the process of informing them and obtaining their consent to this special role in the research will differ from the process used for the treated subjects.

  Satisfactorily addressed in §9.1.6.2 as amended June 14, 2007.

- The process for recruiting, screening, informing, and consenting subjects in Florida should be described in detail comparable to that of the description of the same process in California, with particular attention to the role played in the process by the mosquito control district administration.

  Amendment #4 of June 14, 2007 deleted references to testing in Florida.

In its June 13, 2007, draft final report of the April, 2007 meeting, the HSRB stated its concurrence with EPA's finding that with minor revisions protocol WPC-001 would meet the applicable requirements of 40 CFR 26 subparts K and L. The HSRB report also made the following specific suggestions:

- First, the Board recommended that investigators trap landing mosquitoes or other vectors for pooled serologic or nucleic acid-based testing. Such testing would allow research participants to be warned of their potential exposure to vector-borne pathogens, and allow them to seek appropriate testing and treatment if necessary.

  Amendment #5 of June 14, 2007 added viral analysis of collected mosquitoes.

- Secondly, the Board expressed concerns about plans to recruit research subjects in Florida, as these recruitment procedures were not described adequately in the protocol and supporting materials. If the investigators do not plan to recruit research subjects in Florida, this change should be made in the protocol and consent materials.

  Amendment #4 of June 14, 2007 deleted references to testing in Florida.

- Finally, the Board raised questions about the informed consent procedures for control subjects. Since control subjects would be presented with higher risks than treated subjects, the informed consent procedures should modified to more clearly explain the risks to control (untreated) research subjects.

  Separate consent documents are provided for untreated subjects in amendments of 14 June, approved by IIRB 6/19/07 and further revised (approved on 10 July and 13 July) to resolve language concerning pregnancy risks to untreated subjects.

Regulatory and Statutory Standards

Because this research was initiated after April 7, 2006, the following provisions of 40 CFR 26 Subpart Q, as amended effective August 22, 2006, define the applicable ethical standards, which read in pertinent part:

> §26.1703: Except as provided in §26.1706, . . . EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

> §26.1705: Except as provided in §26.1706, . . . EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part. . . .

In addition, §12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) applies. This passage reads:

> In general, [i]t shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Findings

- *Protocol Review by EPA and HSRB*

  The requirements of 40 CFR §26.1125 for prior submission of the protocols to EPA and of §26.1601 for HSRB review of the protocols were satisfied.

- *Responsiveness to EPA and HSRB suggestions*

  Suggestions by both EPA and HSRB calling for clarification in the SCI-001 protocol of how "experienced subjects" would be recruited to serve as untreated controls were not implemented by changes to the protocol or consent documents after the January HSRB discussion. Given the concurrent execution of the two protocols, it is likely that the actual practice of recruiting untreated subjects in SCI-001 tracked closely to that described in the WPC-001 protocol.

  The suggestion by the HSRB that the consent document for SCI-001 be changed to project up to 48 subjects was not implemented. The actual number of subjects was 37-41, depending on the actual number of untreated control subjects, some of whom were not identified uniquely, but only by function.

  Most other suggestions by EPA and HSRB were implemented responsively.

- *Prohibition of research involving pregnant or nursing women or children*

  The requirement of 40 CFR §26.1703 prohibiting research involving intentional exposure of pregnant or nursing women or of children under 18 was met by both studies.

- *Substantial compliance with 40 CFR 26 subparts A through L*

  40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are applicable to third-party research.

Subpart K, §26.1108(a)(4), reads in pertinent part:

> In order to fulfill the requirements of this subpart each IRB shall:
> (a) Follow written procedures:
> (4) For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

The procedures of the IIRB were not effective in ensuring that the amendments to the SCI-001 protocol changing one of the test repellents from Insect-Guard II to LipoDEET 3434 and adding a viral analysis of collected mosquitoes were not initiated without IRB review and approval. In this case the changes were not necessary to eliminate apparent immediate hazards to subjects. The investigator has explained his understanding that "the PI takes considerable responsibility, and has considerable authority, in determining whether an amendment represents a sufficiently great change to the risk-benefit profile of a study to require additional ethical review." (Communication of September 24, 2007). This understanding appears to be discrepant with the plain language of the rule quoted above.

Subpart K, §26.1116**,** reads in pertinent part:

> No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject.

In executing WPC-001, Subject 29 is reported to have undergone limb measurement on July 7, but to have signed a consent document on July 11. No explanation is provided of this apparent violation of the rule. In the same study, Subject 60 is reported to have participated in dosimetry testing on July 10, but to have signed a consent document on July 12. The investigator says of the latter case "We do not believe that that subject was consented late, but rather that she inadvertently consented anew during a visit to the lab on the 12th, and that that form was then retained rather than her signed form from the 10th."

- *Compliance with 40 CFR §26 subpart M*

  As is documented in Attachments 1 and 2 to this memorandum, the requirement of 40 CFR §26 subpart M to document the ethical conduct of research involving human subjects has been met for both SCI-001 and WPC-001.

- *Compliance with FIFRA §12(a)(2)(P)*

  The requirement of FIFRA §12(a)(2)(P) that human subjects of research be "fully informed of the nature and purposes of the test and of any physical and mental health consequences reasonably foreseeable therefrom," and "freely volunteer to participate in the test," was met for both studies.

Conclusions

These studies meet most applicable ethical standards for the protection of human subjects of research, but I am concerned by several aspects of the conduct of each of them:

SCI-001

- The amendment changing the test material, implemented without IRB review or approval, and the explanation of the investigator's understanding that it is within his discretion to determine which amendments to an approved protocol require the IRB's attention;
- The failure to acknowledge the change of test material in the sub-study reports addressing the unchanged test materials;
- The amendment to add viral analysis of collected mosquitoes, also without IRB review or approval;
- The failure to acknowledge concurrent execution with WPC-001, and the misstatement that "all subjects were wearing the same repellent" on July 12;
- The change in role of the "experienced subjects" to include service as assistants to the investigators, without amendment to the protocol of consent documents, and without IRB review or approval; and
- The compromise of the exclusion factor prohibiting participation in field testing by subjects who had used repellents on the previous day.

WPC-001

- Reporting of a "study initiation date" six days later than the date on which limb measurement of participating subjects is reported to have begun;
- Limb measurement of subject 29 on July 7 before he signed a consent document on July 11;
- Inclusion of subject 60 in the dosimetry phase of testing on July 10 before she is reported to have signed a consent document on July 12;
- Reported signature by untreated controls of the July 13 revised consent document on July 16, the day after the final day of field testing;
- The failure to acknowledge concurrent execution with SCI-001, and the misstatement that "all subjects were wearing the same repellent" on July 12;
- The change in role of the "experienced subjects" to include service as assistants to the investigators, without amendment to the protocol of consent documents, and without IRB review or approval; and
- The compromise of the exclusion factor prohibiting participation in field testing by subjects who had used repellents on the previous day.

The multiple failures to fully report deviations from the protocols, to ensure documented consent is obtained before a subject begins service as a research subjects, and to report all amendments to the IRB represent at least "technical noncompliance" with the cited passages of

subpart K. In my judgment, these shortcomings did not put the subjects at greater risk than they would have faced had the protocols been executed without exceptions, but, taken together with the other deficiencies noted, they may have compromised the studies to the point that even the low risks to the subjects were no longer justified by the information obtained.

I defer to the Human Studies Review Board for guidance concerning whether the instances of noncompliance I have noted in this review rise to the level of "substantial" noncompliance with the requirements of 40 CFR §26 subparts K and L.

Attachments:

1. §26.1303 completeness check for SCI-001
2. §26.1303 completeness check for WPC-001
3. Analysis of Activities by Subject: Carroll-Loye Studies SCI-001 and WPC-001

§26.1303 Submission of Completed Human Research for EPA Review
SCI-001.1 (MRID 47211901), SCI-001.2 (MRID 47208401), SCI-001.3 (MRID 47211801)

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

Requirement			Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y	Satisfied with protocol submission; Amendments 001.2 pp. 212-213 not reviewed by IRB
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of • members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	Satisfied with protocol submission
	§1115(a)(3): Records of continuing review activities.		n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	001.1 pp. 218-219
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	Satisfied with protocol submission
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	Satisfied by prior submission to EPA and assurance of no change
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	Satisfied with protocol submission
		(2) The measures proposed to minimize risks to the human subjects;	Y	Satisfied with protocol submission
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Satisfied with protocol submission
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Satisfied with protocol submission
		(5) The balance of risks and benefits of the proposed research.	Y	Satisfied with protocol submission
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Satisfied with protocol submission
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Satisfied with protocol submission
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	Satisfied with protocol submission
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	See §1115(a)(4) above
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.		Y	Final approval 001.1 pp. 144-145; 156
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	001.1 pp. 157-174
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	

§26.1303 Submission of Completed Human Research for EPA Review
WPC-001 (MRID 47217601)

Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

Requirement			Y/N	Comments/Page References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y	Satisfied in protocol submission; Amendments pp. 113-119 Approved revised consent docs pp. 121-138; 140-157; 159-167
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of • members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.		Y	Satisfied with protocol submission
	§1115(a)(3): Records of continuing review activities.		n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	pp. 219-222
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		Y	Satisfied with protocol submission
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		Y	Satisfied by prior submission to EPA and assurance of no change
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) A discussion of:	(1) The potential risks to human subjects;	Y	Satisfied with protocol submission
		(2) The measures proposed to minimize risks to the human subjects;	Y	Satisfied with protocol submission
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	Satisfied with protocol submission
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Satisfied with protocol submission
		(5) The balance of risks and benefits of the proposed research.	Y	Satisfied with protocol submission
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Satisfied with protocol submission
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	Satisfied with protocol submission
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		Y	Satisfied with protocol submission
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	See §1115(a)(4) above
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.		Y	Approvals pp. 120, 139, 158
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	pp. 140-157; 159-167
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			n/a	

Analysis of Activities by Subject:
Carroll-Loye Studies SCI-001 and WPC-001

Subj/Sex	Limb Measure-ment	Dosimetry		Efficacy Trials					
				Butte County		Glenn County			Butte County
		SCI-001	WPC-001	7 Jul	8 Jul	12 Jul	13 Jul	14 Jul	15 Jul
1 F	11 Jul						Lipo302 R	Duranon R	Lipo3434 R
3 ?	NR			Control					
5 M	11 Jul						Ultrathon L		
6 M	5 Jul		10 Jul						Control
7 F	5 Jul	5 Jul							
8 M	6 Jul		10 Jul	Duranon ?	Lipo3434 ?	Lipo302 ?	Ultrathon ?	Duranon ?	OLE R
10 M	5 Jul			Duranon L					
13 M	3 Jul	3 Jul		Duranon ?	Ultrathon ?	Control	Control		Control
14 M	5 Jul	5 Jul	10 Jul	Control		Control	Control		Lipo3434 ?
15 M	5 Jul	5 Jul		Ultrathon L			OLE L	Lipo3434 L	OLE L
17 F	11 Jul		11 Jul						OLE L
18 M	11 Jul					Duranon L	Lipo3434 L	Lipo302 L	Lipo302 L
20 F	11 Jul						Lipo302 R	Ultrathon R	OLE R
21 M	11 Jul						Lipo302 L	Ultrathon L	OLE L
22 M	11 Jul								Lipo302 R
24 M	5 Jul		10 Jul	Ultrathon L		Lipo3434 L			
25 F	11 Jul								Lipo302 R
27 F	5 Jul	5 Jul							
28 F	7 Jul					Lipo3434 ?			
29 M	7 Jul								OLE L
32 M	5 Jul				Lipo3434 R				
36 F	11 Jul					OLE R			
37 F	4 Jul	4 Jul	10 Jul	Ultrathon L		Lipo3434 L	OLE L		
38 F	11 Jul					OLE L			
39 F	7 Jul			Lipo302 R	Ultrathon R				Lipo3434 R
40 F	6 Jul			Lipo302 ?	Lipo3434 ?	Duranon ?	OLE ?	Lipo302 ?	Duranon ?
43 M	10 Jul					Lipo3434 L	OLE L		
46 M	10 Jul					Duranon R	Lipo3434 R	Ultrathon R	Ultrathon R
52 M	5 Jul			Lipo302 L	Duranon L	OLE L		Lipo3434 L	Ultrathon L
53 F	5 Jul			Lipo302 L	Duranon L	OLE L	Ultrathon L	Lipo3434 L	Ultrathon L
56 F	4 Jul	4 Jul							
57 M	5 Jul	5 Jul							
60 F	5 Jul	5 Jul	10 Jul	Lipo3434 L	Lipo 302 L	Duranon L	OLE L		
61 F	5 Jul	5 Jul	10 Jul	Lipo3434 L	Duranon L	Ultrathon L			
62 F	6 Jul		10 Jul			Lipo302 L			Lipo302 L Lipo3434 L
63 M	6 Jul			Lipo3434 L	Duranon L	Lipo302 L	OLE L	Duranon L	Ultrathon L
64 M	6 Jul			Lipo3434 ?					
67 M	7 Jul		10 Jul		Lipo302 R	Ultrathon R	Duranon R		OLE R
68 F	8 Jul				Ultrathon L				Duranon L
69 F	8 Jul				Duranon R				OLE R
70 F	13 Jul						Lipo3434 L		
71 M	10 Jul					Ultrathon ?	Duranon ?	Lipo302 ?	OLE L
72 M	10 Jul					Ultrathon R	Duranon R	Lipo302 R	OLE R
C1 ?	NR				Control			Control	
C2 ?	NR				Control			Control	

Notes to Attachment 3:

1. Each treatment is identified in the table by a color code. Colored entries in the "Limb Measurement" column indicate that the limb measurements for that subject were only reported in the study report associated with the color. In the cells indicating participation in the field efficacy trials, the color indicates the treatment by that subject on that day.

2. The entry ("R", "L", or "?") to the right of the treatment name indicates which leg was treated. This was reported directly for WPC-001 (pp. 26-29). The treated leg was not reported in any of the three reports for SCI-001, but could be inferred in most cases by comparing the treated area (SCI-001.1 p. 37, SCI-001.2 p. 38, and SCI-001.3 p. 38) with the reports of measurements for each subject contained in Appendix 6 of each volume. When the measured area of a subject's left and right legs was the same, the identity of the treated leg could not be inferred. In all cases where the identity of the treated leg was reported or could be inferred, treatment of each subject was invariably to the same leg every time that subject participated in field testing.

3. Forty-three subjects (20 ♀, 22 ♂, plus subject #3, whose sex was not reported) are identified by subject number in one or more of the four study reports. The subjects who served as untreated controls on 8 July and 14 July were not identified by number; they could bring the total number of subjects involved up as high as 47, but it seems likely that the control subjects on those two days were selected from the same small group that served in that capacity on the other four test days—subjects 3, 6, 13, and 14.

4. Subject 62 is reported to have been treated with both LipoDEET 302 and LipoDEET 3434 on the same leg on 15 July. See SCI-001.1 p. 37 and SCI-001.2 p. 38.

5. Two subjects (3, 6) served only as untreated controls in the efficacy phase, although subject 6 also participated in the dosimetry phase of WPC-001. Two subjects (13, 14) served both as untreated controls, as treated subjects in SCI-001, and participated in dosimetry testing for all four materials in SCI-001. Subject 14 also participated in dosimetry testing for WPC-001. Four more subjects (7, 27, 56, and 57) participated only in the dosimetry phase of SCI-001.

6. Sixteen subjects (1, 5, 10, 18, 22, 24, 25, 28, 32, 39, 46, 61, 62, 64, 68, and 70) served as treated subjects only for SCI-001, although three of them (24, 61, and 62) also participated in dosimetry testing for WPC-001, and one (61) in dosimetry testing for all four materials in SCI-001.

7. Four subjects (17, 29, 36, and 38) served as treated subjects only for WPC-001. One of them (17) also participated in dosimetry testing for WPC-001.

8. Fifteen subjects (8, 15, 20, 21, 37, 40, 43, 52, 53, 60, 63, 67, 69, 71, and 72) served as treated subjects in both WPC-001 and SCI-001. Five of these also participated in dosimetry testing: three (15, 37, and 60) for SCI-001 and four (8, 37, 60, and 67) for WPC-001.

9. On 7 July 16 subjects participated in field testing at the site in Butte County. Subjects 13 and 14 served as untreated controls. Three subjects were treated with Duranon (8, 10, and 13); three with Ultrathon (15, 24, and 37); four with LipoDEET 302 (39, 40, 52, and 53) and four with LipoDEET 3434 (60, 61, 63, and 64). No field testing of OLE occurred on this date.

10. On 8 July 15 subjects participated in field testing at the site in Butte County. Two unidentified subjects served as untreated controls. Five subjects were treated with Duranon (52, 53, 61, 63, and 69); three with Ultrathon (13, 39, and 68); two with LipoDEET 302 (60, 67); and three with LipoDeet 3434 (8, 32, and 40). No field testing of OLE occurred on this date.

11. On 12 July 21 subjects participated in field testing at the Glenn County site. Subjects 13 and 14 served as untreated controls. Four subjects were treated with Duranon (18, 40, 46, and 60); four with Ultrathon (61, 67, 71, and 72); three with LipoDEET 302 (8, 62, and 63); four with LipoDEET 3434 (24, 28, 37, and 43); and four with OLE (36, 38, 52, and 53).

12. On 13 July 20 subjects participated in field testing at the Glenn County Site. Subjects 13 and 14 again served as untreated controls. Three subjects were treated with Duranon (67, 71, and 72); three with Ultrathon (5, 8, and 53); three with LipoDEET 302 (1, 20, and 21); three with LipoDEET 3434 (18, 46, and 70); and six with OLE (15, 37, 40, 43, 60, and 63).

13. On 14 July 15 subjects participated in field testing at the Glenn County Site. Two unidentified subjects served as untreated controls. Three subjects were treated with Duranon (1, 8, and 63); three with Ultrathon (20, 21, and 46); four with LipoDEET 302 (18, 40, 71, and 72); and three with LipoDEET 3434 (15, 52, and 53). No field testing of OLE occurred on this date.

14. On 15 July 25 subjects participated in field testing at the Butte County Site. Subjects 6 and 13 served as untreated controls. Two subjects were treated with Duranon (40, 68); four with Ultrathon (46, 52, 53, and 63); four with LipoDEET 302 (18, 22, 25, 62); four with LipoDEET 3434 (1, 14, 39, and 62); and ten with OLE (8, 15, 17, 20, 21, 29, 67, 69, 71, and 72).

15. Field testing took place on six different days. Four subjects (7, 27, 56, and 57) did not participate at all in field testing. Fourteen subjects (3, 5, 6, 10, 17, 22, 25, 28, 29, 32, 36, 38, 64, and 70) participated in only one day of field testing. Five subjects (24, 43, 62, 68, and 69) participated in two days of field testing; six subjects (1, 20, 21, 37, 39, and 61) participated on three days; eight subjects (14, 15, 18, 46, 60, 67, 71, and 72) participated on four days; two subjects (13, 52) participated on five days; four subjects (8, 40, 53, 63) participated on all six days. On average, each of the 39 subjects who participated in at least one day of field testing participated in 2.8 days of testing.