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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 14, 2007

MEMORANDUM

SUBJECT: Ethics Review of EMD-003.3 Report of Completed Efficacy Study for Aerosol Tick Repellent Containing IR-3535

FROM: John M. Carley
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TO: Linda Hollis, Chief
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REF: Carroll, S. (2007) Test of Personal Insect Repellents. Unpublished study prepared by Carroll-Loye Biological Research under Project No. EMD-003.3 (Aerosol). 143 p. (MRID 47045901)

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced document, which describes a single execution of the protocol EMD-003, a laboratory test of the efficacy of IR-3535 formulations in repelling ticks.

Background

After its first review and approval by the Independent Investigational Review Board (IIRB) of Plantation FL, this protocol was initially submitted to EPA by Carroll-Loye Biological Research in the Spring of 2006. Both EPA and the HSRB found the protocol to require significant revision before it could be approved. Following the HSRB discussion of EMD-003 in June, 2006, the Principal Investigator, Dr. Scott Carroll, revised it substantially, resubmitted it to the IIRB (who approved it again) and resubmitted it to EPA. After this revision EPA found the protocol to meet all ethical requirements of 40 CFR 26 subparts K and L. The HSRB reconsidered EMD-003 at its October 2006 meeting, and concurred with EPA's assessment, with minor comments.

As reviewed, the protocol called for testing three different formulations of the repellent ingredient IR-3535: a lotion, a pump spray, and an aerosol. Dosimetry testing of all three formulations was initiated on October 23, 2006. An error in formulation of the aerosol was discovered, however, that led to deferral of efficacy testing of the aerosol. Testing of the lotion and pump spray formulations went forward, and reports of that testing were reviewed by the HSRB in January, 2007.

Scope of Review

This review covers the revised report of executing protocol EMD-003 with the aerosol formulations. The following specific documents were considered:

- Revised study submission of February 5, 2007: MRID 47045901
- EPA's Protocol Review of September 15, 2006

  Carley, J., and Fuentes, C. (2006) Science and Ethics Review of Protocol for Human Study of Tick Repellent Performance. Memorandum to Sheryl Reilly dated 9/15/2006. 14 p.

- Final Report of October 18-19, 2006 Meeting of the Human Studies Review Board

Completeness of Submissions

The standard of completeness for documenting ethical conduct of completed research submitted to EPA under the pesticide laws is defined by 40 CFR §26.1303. This passage tracks closely to the standard for documenting protocols, but requires only submission of materials "not previously provided to EPA." Most of the requirements of this regulation were satisfactorily addressed at the time of protocol submission, and need not be addressed again.

The submitted study was accompanied by an apparently complete record of correspondence between the sponsors or investigators and the IIRB after the October HSRB meeting.

Section 26.1303(c) requires "[c]opies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research." While the study reports do contain copies of the Informed Consent Document as approved by the IIRB on November 1, it is not clear what records were actually used to document subject consent, since data collection in the dosimetry phase of the research had been completed before the revised protocol was submitted to the IIRB and before approval of the ICF included in the report. The approval letter states "[a]ll current subjects and future volunteers must sign the revised consent form." Although the study reports state "[s]ubjects . . . signed the IRB approved Informed Consent Form," it is not clear which generation of the approved form was signed, or how many generations of the form were signed, or when they were signed.

The checklist used by EPA to verify satisfaction of the requirements of §26.1303 appears

as Attachment 1 to this memorandum.

Protocol Deviations

Several minor deviations from the protocol are reported in Appendix 5. None affected the integrity of the research or the safety of the subjects.

Although it was not reported as a deviation from the protocol, data collection was initiated before either QA review of the protocol or IRB approval of the final round of changes to the protocol and Informed Consent Form. This is discussed further below.

Applicable Ethical Standards

Because this research was initiated after April 7, 2006, 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.

The final report of the October 18-19, 2006 HSRB meeting stated the Board's concurrence with EPA's finding that the protocol as revised met all ethical requirements of 40 CFR 26 subparts K and L, and made two specific suggestions:

- "The Board recommended, however, that the nature and likelihood of any side effects or adverse events be clearly described in the informed consent documents."

- "Carroll-Loye Biological Research also may wish to designate a specific physician to be contacted in the event that any adverse side effects are seen."

Because this research was conducted 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, Section 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 §26.1125 for prior submission of the protocol to EPA and of §26.1601 for HSRB review of the protocol were met.

- Revisions to the protocol and Informed Consent Form.

  Subsequent to the October 18 HSRB discussion of this protocol the Investigator amended the discussions in the Informed Consent Form of "Risks/Discomforts" and "Pregnancy Risks" to clarify the nature and likelihood of potential side effects or adverse effects. In addition, as suggested by the Board, the discussion of "Research Related Injuries" in the Informed Consent Form was expanded to note that in the event of an injury, "a consulting physician who is aware of the study will be contacted immediately by telephone." Additional changes were made to the protocol itself responsive to the Board's discussion.

  The revised protocol and Informed Consent Form were submitted to the Independent Investigational Review Board as proposed changes to previously approved research, probably on October 24, and approved, apparently after submission of additional information (the "Site letter of 10/30") to IIRB, on November 1.

  The procedures of the IIRB governing "Modifications of Ongoing Research" require the investigator to report changes promptly, and to await Board approval before implementing modifications unless they are necessary to eliminate immediate hazards.

  The Carroll-Loye QA unit conducted its protocol review on October 26. The protocol (Section 13, Quality Assurance) states in pertinent part:

  > Protocol Review and Comments must take place before data collection commences.

  The dates on the data recording forms presented with the study report show that the dosimetry phase of data collection was initiated on October 23, before either the IIRB approval of modifications and QA review of the revised protocol, and the repellency testing phase of data collection was conducted on November 18, after QA review of the protocol and IIRB approval of the modifications to the protocol and Informed Consent. As was discussed at the HSRB meeting in January 27 with respect to the execution of this protocol for the other two formulations, the investigator erred in implementing changes to the Informed Consent with handwritten corrections before receiving IIRB approval, nor did he meet his obligation to report all deviations to the IIRB. These errors are

serious, and steps must be taken to ensure they do not happen again. Nonetheless they did not put subjects at increased risk, nor did they compromise the consent process.

- Ban on research involving pregnant or nursing women or children

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

- Compliance with 40 CFR 26 subparts A through L

  Section 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.

  As is noted above, data collection for this research was both initiated and completed before IIRB approval of the final round of changes in the protocol and Informed Consent Form. 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, cited above, were not effective in ensuring that changes in approved research were not initiated without IRB review and approval. In this case the changes were not necessary to eliminate apparent immediate hazards to subjects. They had at most a very minor effect on the quality of information provided to subjects, or on the safety of the subjects.

- 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.

Conclusion

This study meets most applicable ethical standards for the protection of human subjects of research, but I am concerned both by the investigator's initiating the research before receiving IIRB approval of revisions to the protocol and Informed Consent, and by his failure to acknowledge doing so in the report of the research. Using consent forms with handwritten changes not approved by the IIRB for the dosimetry phase was a violation of IIRB procedures;

those IIRB procedures, in turn, are required by the Common Rule and by 40 CFR §26.1108(a)(4). The failure to timely and fully report deviations to the IIRB and to acknowledge them in the study report represents at least "technical noncompliance" with the cited passages of subpart K. In my judgment, however, the available evidence supports the conclusion that the "research was conducted in substantial compliance" with subparts K and L.

Attachment: §26.1303 completeness check

40 CFR §26.1303 Submission of Completed Human Research for EPA Review
EMD-003.3: MRID 47045901

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 rlevant 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
	§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	
	§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 with protocol submission
	§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 reported p. 76
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			N	ICF on pp. 77-83 shows IIRB approved 11/1; dosimetry data collection began 10/23. Unclear what ICF was actually used at each stage of the research.
(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	