UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 24, 2007

SUBJECT: Science and Ethics Review of Protocol for Human Study of Tick Repellent Performance

FROM: John M. Carley
Human Research Ethics Review Officer

Kevin Sweeney,
Science Reviewer

TO: Marion Johnson, Chief
Insecticide Branch, RD

REF: Carroll, S. (2007) Efficacy Test of Picaridin-Based Personal Tick Repellents: Efficacy Test Protocol SPC-002, dated June 10, 2007. Unpublished document prepared by Carroll-Loye Biological Research. 70 p. (MRID 47182202)

We have reviewed the referenced protocol for a laboratory test of tick repellency from both scientific and ethics perspectives. This review assesses the scientific aspects of the proposed research in terms of the recommendations of the draft EPA Guidelines 810.3700 and of the EPA Human Studies Review Board, and the ethical aspects of the proposed research in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 5. IRB procedures are on file at EPA, and need not be resubmitted. All required elements are present.

In addition to the protocol itself (pp. 3-35) and the associated consent document (pp. 39-45), the following supporting documents were considered in this review:

- IIRB Approval letter of 7/17/07 (pp. 36-37)
- Selected data collection forms (pp. 46-50), not including a form for collecting efficacy data in the field
- Subject training materials for spray dosimetry and tick handling (pp. 51-56)
- MSDSs for test products (pp. 57-62)
- Site Questionnaire: SPC-002 (pp. 63-66)
- Study Specific Instructions: SPC-002 (p. 67)
- Email correspondence between Carroll-Loye Biological Research and Independent Investigational Review Board (pp. 68-70)
- Roogow, R. (2007) RE: Meeting minutes for SPC-001 & SPC-002/Procedures & membership. July 26, 2007 E-mail message to John Carley and attached minutes of IIRB meeting on July 17, 2007. 3 p.

B. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of our observations about the ethical aspects of the proposed protocol. Supporting details are in the attachment.

1. **Societal Value of Proposed Research:** This study will test the efficacy against ticks of two registered repellent sprays containing the active ingredient picaridin, and of one lotion formulation including both picaridin and a sunscreen, for which an application for registration is pending. EPA requires efficacy data to support continued registration of several products owned by this sponsor, and has agreed to a testing plan reflected in this protocol. EPA requires testing of the lotion product to support the pending registration application. Testing of the duration of efficacy is important because consumers, who rely on repellents to avoid tick bites, cannot readily assess the efficacy of a product independent of EPA's approval. There is potential benefit to society in demonstrating effectiveness of picaridin repellents at these concentrations and in these forms, which users may prefer to other repellent products because of their cosmetic or other qualities.

2. **Subject Selection:** Subjects will be recruited from a "Volunteer Database" of previous subjects and others who asked to be added to the database. The database is racially diverse, 75% in the age range from 20-40 and 25% in the range 40-55. The relative youth and high education levels of candidates in the database reflect the university community where the laboratory is located. Explicit factors exclude as subjects children, pregnant or lactating women, those in poor health or physical condition, and those unable to speak and read English. The sample will thus not be fully representative of the population of potential repellent users. There is no indication that any subjects will be from vulnerable populations.

   Subjects will be compensated for their participation at a rate of $20/hour. A subject who participated in both the dosimetry phase (2-2.5 h) and repellency testing for one formulation (8-14 h) would be compensated at $200-$330. A subject who participated in the dosimetry phase and repellency testing for all three formulations would be compensated at $520-$890.

3. **Risks to Subjects:** Risks of three kinds are identified: risks from exposure to the test material, risks of exposure to biting arthropods, and risks of exposure to arthropod-borne disease. The test material is accurately characterized in the consent form as an eye irritant, harmful if swallowed—consistent with the required hazard statements on the registered product labels.

   All practical steps to minimize subject risks have been taken:

   - Risks from exposure to the test materials are minimized by excluding candidates with known sensitivity to product ingredients, by monitoring subjects closely during the dosimetry phase of the research, and by applying materials in the repellency phase by technicians.

   - Risks from arthropod bites are minimized by training subjects to handle and observe ticks, so they can be removed before they have time to bury or bite.

   - Risks of contracting disease are minimized by the same means used reduce the risk of bites, and by using laboratory-raised, pathogen-free ticks.

   Because of the generally low acute and chronic hazard profile of the material, the design of the research to minimize exposure, and the training of subjects to remove ticks before they have time to bury or bite, the probability of the identified risks is accurately characterized as “extremely small”.

   The risks of tick bites and of exposure to tick-borne disease, although mentioned in the protocol, are not addressed in the consent document. The measures to be implemented to ensure ticks don’t bury and bite, and by whom they would be implemented, are not explained. Both these deficiencies should be corrected.

   Although neither the protocol nor the consent document discusses potential psychological risks or risks of embarrassment associated with the requirement that female candidates take a pregnancy test, the research is designed to minimize these risks as well.

4. **Benefits:** The protocol and consent are clear that there are no direct benefits to subjects. The protocol acknowledges that the sponsor will benefit from continued registration of the tested products and of the similar products to which the results of this research will be extrapolated, but discussion of benefits is otherwise weak. Assuming eventual regulatory approval, indirect beneficiaries may also include repellent users who prefer these products to other repellents.

5. **Risk/Benefit Balance:** No practical opportunities to further reduce risk to subjects while maintaining the robustness of the scientific design have been overlooked. The residual risk to subjects is very low, and is reasonable in light of the potential benefits to repellent users, which are likely to be realized.

6. **Independent Ethics Review:** The Independent Investigational Review Board, Inc., of Plantation FL has reviewed and approved the protocol and informed consent materials. The IIRB is independent of the investigators and sponsors. Documentation of IIRB procedures was not submitted with this protocol, but a statement was made by the IIRB that this information had not changed since it was previously submitted to EPA.

7. **Informed Consent:** The protocol contains a satisfactorily complete description of the process by which potential treated subjects will be recruited and informed and for seeking their consent to participate. A copies of the IRB-approved consent form meeting all requirements of 40 CFR §§26.1116 and 26.1117 is included in the protocol.

8. **Respect for Subjects**: Methods proposed for managing information about prospective and enrolled subjects are adequate to protect their privacy from compromise. Subjects will be free to withdraw at any time, and will be reminded of this at several points before and during the research. Subjects who withdraw will be compensated for time spent up to the point of withdrawal. Medical care for research-related injuries will be provided at no cost to the subjects.

C. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. Because the test will be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 apply as well, including provision to subjects of the "Experimental Subject's Bill of Rights" appearing on p. 38. A point-by-point evaluation of how this protocol addresses the requirements of 40 CFR 26 Subparts K and L and the criteria recommended by the HSRB is appended as Attachment 1.

These specific deficiencies should be corrected before the research is initiated:

- A data collection form suitable for recording the actual efficacy testing should be added to the forms set provided.

- The approved product labels for the test materials (or the proposed label for the lotion still pending registration) should be included in the protocol and made available to the subjects, specifically in the dosimetry phase, so that they can do their best to follow label directions when applying a "typical consumer dose."

- The risks of tick bites and of exposure to tick-borne disease, mentioned in the protocol, are not addressed in the consent document. The measures to be implemented to ensure ticks don't bury and bite, and by whom they would be implemented, are not explained. Both these deficiencies should be corrected.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> 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.

This protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

D. Summary Assessment of Scientific Aspects of the Proposed Research

The study will test the efficacy under laboratory conditions as a tick repellent of two registered repellent spray products containing picaridin, and one picaridin/sun-screen lotion for which an application for registration is pending. The main objective of the study is to quantify the efficacy of the formulations to repel actively questing ticks. A secondary objective of the study is to characterize through dosimetry testing the amount of each formulation typically self-applied by consumers.

Active questing behavior of each tick will be verified by placing each tick on the untreated forearm of the subject. Ticks which do not move ("quest") in the direction of the elbow at least 3 cm within 3 minutes will not be used in the efficacy trial. Qualifying ticks will be placed one at a time on the wrist of the subject's treated arm, and monitored for 3 minutes to determine whether they cross into the treated area of the arm or are repelled by the test material. The cycle of qualifying a tick on the untreated arm and then testing qualified ticks for repellency on the treated arm is repeated every 15 minutes from the time of application of the test material until efficacy failure, defined as a crossing into the treated area followed by another crossing within either of the two subsequent test periods.

1. **Study design:** The protocol has two objectives: to test the tick repellent efficacy of the three picaridin formulations, and to establish a typical consumer dose for each product, to be used as the standard dose in the efficacy phase. These objectives can be met by the study as proposed.

2. **Statistical design:** The sample size of 10 treated subjects for each test material is larger than is required by EPA guidelines—large enough to ensure robust averages across subjects, but small enough to be economical. Each subject is treated on one forearm only; the untreated forearm serves as a control to confirm active questing behavior of each tick. No positive control or negative vehicle control is proposed. Because the lotion and spray test materials are obviously different, efficacy testing will not be blinded. Repellency will be reported as "Complete Protection Time", calculated for each test material as the mean time across all treated subjects from application of the repellent to the First Confirmed Crossing. Time of each crossing will be reported with a precision of 15-minute intervals; the average time across all subjects from treatment until First

Confirmed Crossing will be calculated, with standard deviation and 95% confidence interval.

3. **How and to what will human subjects be exposed?** In the initial dosimetry phase, subjects' lower arms will be repeatedly exposed for a few minutes each time to the test materials to estimate a "typical consumer dose." In the repellency phase the standardized typical dose, expressed as volume per unit area, is scaled to the measured surface area of each subject's forearm and applied by a technician to the subject's forearm. The repellent will remain in place for 8 to 14 hours during the test. In addition, subjects in the efficacy phase will be exposed to potential bites by lab-reared pathogen-free ticks (with very low probability), and (with extremely low probability) to arthropod-borne diseases.

4. **Endpoints and Measures:** In the dosimetry phase the applied dose will be expressed as mass per unit area; a "typical consumer dose" will be calculated for each formulation as the grand mean of individual mean doses applied. This standard unit dose will be used for each subject in the repellency phase. In the repellency phase, complete protection time (CPT) will be measured as the mean time from initial application of a typical consumer dose to the First Confirmed Crossing (FCC), and will be presented with standard deviation and 95% confidence interval. Subjects will be trained in the laboratory to handle ticks and observe their behavior, and to remove ticks before they have time to bury or bite. All crossings will be recorded by a research technician and included in the report of the research.

E. Compliance with applicable Scientific standards

This protocol adequately addresses the following elements according to applicable scientific standards:

- Scientific objectives
- Experimental design for achieving objectives
- Methods for estimating dose of test material
- Quantification of efficacy of the test materials
- Data collection, compilation and summary of test results
- Discussion of the statistical power of the study.
- Justification for sample size in dosimetry and repellency phases
- Rationale for use of two untreated negative control subjects to monitor biting pressure.

This protocol does not adequately address the following elements:

- The protocol does not adequately characterize the composition of the lotion product. This product is pending registration and EPA knows the complete product composition.

- This protocol does not report the source(s) of the ticks used in this study. The American dog tick, *Dermacentor variabilis*, is a vector of Rocky Mountain Spotted Fever (RMSF). Unlike Lyme disease, RMSF can be transmitted from one tick generation to another

transovarially. The study design makes the likelihood of a tick bite quite low, but assurance is needed that the ticks are RMSF-free, should a subject be bitten. What would the Study Director do should this occur?

Attachments:

1. Summary Review of Carroll-Loye Protocol SPC-002 dated 7/10/2007
2. §26.1111 Criteria for IRB approval of research
3. §26.1116 General requirements for informed consent
4. §26.1117 Documentation of informed consent
5. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Protocol Review: SPC-002

Title: Efficacy Test Protocol #SPC-002: Efficacy Test of Picaridin-Based Personal Tick Repellents

Date: 10 July 2007

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1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

"The objective of this study is to test the repellent efficacy characteristics of the test materials to ticks. . . . The general hypothesis of the research is that the test materials will substantially reduce the probability that a tick crosses a repellent treatment for several hours. However, more than testing that hypothesis, the aim of the research is to characterize the duration of repellency based on the Complete Protection Time criterion. Complete Protection Time . . . is defined herein as the time between application of test material and the First Confirmed Crossing.'" (p. 4)

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

"This study will test the efficacy of three [registered] formulations" containing picaridin, for which EPA has required that additional efficacy data be collected. (p. 4)

(c) How would the study be used by EPA?

EPA will consider the study in defining acceptable label claims for repellent efficacy for the test materials and other closely related formulations to which the results of this research can be extrapolated.

(d) Could the research question be answered with existing data? If so, how? If not, why not?

"As part of its review of Spectrum's Picaridin formulations, the U.S. EPA has specified additional efficacy data to be collected. . . ." (p. 4) Existing data are inadequate to meet EPA's regulatory standards for acceptable data to support label claims of efficacy.

(e) Could the question be answered without newly exposing human subjects? If so, how? If not, why not?

"Human subjects are . . . the target system for the test material, and sufficiently reliable replacement models for repellency testing do not exist. In addition, subjects will self-administer the test articles during dose determination." (p. 5)

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

"The objective of this study is to test the repellent efficacy characteristics of the test materials to ticks. . . . The general hypothesis of the research is that the test materials will substantially reduce the probability that a tick crosses a repellent treatment for several hours. However, more than testing that hypothesis, the aim of the research is to characterize the duration of repellency based on the Complete Protection Time criterion. Complete Protection Time . . . is defined herein as the time between application of test material and the First Confirmed Crossing.'" (p. 4)

"Determining dosage is part of this study's main objective. Dosage for repellency testing will be the mean of the subject means determined . . . in the dosimetry portion of this study." (p. 8)

(b) Can the study as proposed achieve that objective or test this hypothesis?

The two objectives cited above can be achieved by the study as proposed.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

"In both dosimetry and efficacy testing, we will engage 10 subjects per treatment. Each subject is a replicate. It is possible that a single set of 10 individuals could complete all parts of the study. It is much more likely that substantially more than 10 individuals will participate." (p. 14)

The rationale for this sample size appears on pp. 14-17. A sample size of 10 reflects a compromise between cost and precision; it is larger than the minimum of 6 required by EPA, and promises to provide an acceptably robust measure of average Complete Protection Time at reasonable cost.

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

"Dosimetry testing requires an untreated control for the assumption that dosimeters will not gain appreciable weight from contact with untreated skin." (p. 9) "The 'negative control' for efficacy data sets serves to insure that each tick employed in the study is attracted to the test subject before it is used in a repellency challenge. Ticks that fail to meet the questing criterion (§8.4.1) are not used against Test Materials. In this way the negative control serves as a pre-screening of the ticks, such that only actively questing ticks are then exposed to the treatments. Based on this manipulation of a standard control design, the crossing rate on the negative control is judged to be 100%." (p. 9) "There is no control in which each formulation matrix without the repellent active [ingredient] is tested." (p. 9) There are no positive controls. This use of untreated controls to confirm active questing behavior of all ticks used in efficacy testing is appropriate for the study design. Omission of matrix and positive controls is appropriate for the study design. No direct comparisons of treated and untreated subjects (or arms) are contemplated in the statistical analysis plan.

(d) How is the study blinded?

The study is not blinded. (p. 22)

(d) What is the plan for allocating individuals to treatment or control groups?

"For efficacy testing of each test material, each subject is treated on an arm, and has the other arm untreated in order to assess the questing sufficiency of each tick prior to testing it on the untreated arm" (p. 11) *[The next-to-last word should be "treated."]* "The dosimetry study is an examination of dosing behavior for each test material. In that study, each subject will be treated, and will also serve as his or her own untreated control for the dosimeters." (p. 11)

(e) Can the data be statistically analyzed?

Yes. The dosimetry phase provides for three applications of each test material per limb per subject. The three values per limb will be averaged for each subject, and from those individual means the grand mean across all 10 dosimetry-phase subjects will be calculated for each test material.

In the efficacy phase ten individual subject values for CPT will be obtained for each test material and averaged. Although it is possible that the study design could be fulfilled with only ten subjects, it is likely there will be substantially more. No

analysis of repeated measures is contemplated in the case that a single subject participates in more than one phase of the research.

(f) What is the plan for statistical analysis of the data?

"Statistics will be computed with SAS's JMP software, Version 5.0.1.2 (SAS Institute, Cary, NC)." (p. 28)

For the spray formulation, the typical consumer dose will be calculated in the dosimetry phase from the average amount of product (in grams) delivered by subjects and captured by 4 evenly-spaced gauze 'bracelets' on the subject's forearm or lower leg. The surface area of subject's limbs is calculated as the product of the length of the limb by the average of 4 evenly-spaced circumferences. The dosimeter 'bracelets' are 2.5 cm wide, and centered on the points at which the circumferences of the limb were measured. The surface area of the dosimeters is 4 times the average limb circumference (in cm) times 2.5 cm. The unit dose in g/cm^2 applied to the dosimeters is calculated as the weight difference in the dosimeters before and after application divided by the area of the dosimeters. (Calculation of overall unit dosage in the dosimetry phase is unnecessarily complicated by scaling up from the area of the dosimeters to the full skin area of the treated limb; this does not add any precision to the calculation of the applied dose.) Once calculated, the grand mean unit dose in g/cm^2 is divided by the specific gravity of the formulation to obtain a standard volumetric unit dose in ml/cm^2. This is scaled up to the volumetric dose appropriate for the treated limb of each subject in the efficacy phase, based on the surface area of the limb to be treated. (pp. 24-26, 28-29)

In the dosimetry phase, "the amount of lotion applied to the limbs will be quantified in a series of 3 applications analogous to the Spray Sampling. . . . However, dosimeters are not required, nor are the extensive practice sessions. The amount applied is the weight difference in the dispensing tube before and after application." (p. 25)

"Subject effects on dosing behavior will be examined with non-parametric tests for *n*-sample independent cases (Kruskal-Wallis tests). In multiple regression analysis, the average amount of test material intercepted by each subject's dosimeters, as well as dosing per unit skin surface area, will be examined in relation to the distance from nozzle to skin, the number of times the pump was actuated, and limb size. The relationship between dosing behavior and dosage will also be examined with Spearman-rank correlation tests." (p. 29)

In the efficacy phase "Complete Protection Time (CPT) is measured as the length of time from initial application to the First Confirmed Crossing. A FCC is a Crossing followed by another Crossing within 30 minutes. . . . CPT measured in this way will yield a single time value for each subject. Mean CPT will be calculated across all 10 subjects, and will be presented with standard deviation and 95% confidence interval.

"Because all subjects serve as untreated controls to verify tick questing sufficiency, Relative Protection (RP) may also be calculated. Its utility is limited to the time period from first exposure until the first subject testing a given repellent is withdrawn by invoking the Stopping Rule (after which continued calculation of RP would likely bias its value in favor of repellency)." (p. 30)

"To further improve the utility of the data set, we propose to use Kaplan-Meier estimates of the survival function of repellency with time since application (Complete Protection Time). Kaplan-Meier analyses provide median estimates with substantially reduced error estimates compared to means and standard deviations; in particular, they are much less sensitive to data censoring. Moreover, they do not rely on assumptions of data normality. Combining a much larger sample with the Kaplan-Meier estimate of repellent survival improves our ability to estimate the true temporal performance function of test materials in the population." (pp. 31-32)

(g) Are proposed statistical methods appropriate to answer the research question?

The proposed statistical measures for dose determination and duration of repellency are appropriate, and robust enough to be appropriate for either normally or non-normally distributed data.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

Yes. It will produce a data set more robust than most on which past decisions by EPA concerning acceptable claims of repellency have been based.

2.2 How and to what will human subjects be exposed?

(a) What is the rationale for the choice of test material and formulation?

Two of the three test materials are registered by EPA as Reg No. 121-89 (7% Picaridin Pump Spray) and 121-91 (15% Picaridin Pump Spray). Results from testing of these two materials will be extrapolated to support additional registered products held by the same registrant which contain similar concentrations of Picaridin. (See MSDSs pp. 74-79) Efficacy data to support label claims for these products was required by EPA as a condition of the products' continued registration; EPA has agreed to the testing and extrapolation strategy summarized on p. 1 of this protocol.

The third test material is a lotion containing a sun-screen as well as picaridin; it is thus likely to behave differently from the picaridin sprays and wipes, and must be tested separately. An application for registration of this material is pending, and EPA requires product-specific efficacy data to support the pending application and to determine appropriate label claims. No MSDS is provided for this formulation.

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

A "typical consumer dose" will be estimated in the dosimetry phase for each test material as the average quantity of product applied per unit area of treated skin by ten subjects. This standard unit dose will be used for all subjects in the efficacy phase. One limb (forearm or lower leg) of each subject will be treated; exposure to the repellent will be continuous throughout the period of the efficacy test.

Subjects will be exposed for approximately six of every 15 minutes during the efficacy phase to disease-free laboratory-reared deer ticks (*Ixodes scapularis*) and American dog ticks (*Dermacentor variabilis*). (p. 10)

(c) What duration of exposure is proposed?

Participants in the dosimetry phase will experience repeated brief exposures to each test material over a period of about two hours. The repellency phase will last for 8-14 hours; the period of actual exposure is uncertain and will vary by subject, depending on the individual value of CPT.

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

"Variables to be measured" are listed in §10.1. They include "Subject forearm surface area, subject self-dosing behaviors, weight of test materials delivered to the surrogate skin (gauze) dosimeters, and number of tick crossings on the treated surface of the skin." (p. 23)

These are appropriate endpoints to measure, but the list should include weight of lotion delivered to the skin in the dosimetry phase as described in §10.3.4. Clarity would be improved if the language were consistent between this listing and the discussion of each measure in §§ 10.4.1, 10.4.2, 10.4.3, 10.4.4, and 10.4.5.

In addition §10.4.1 *[which is mis-indexed; it should be §10.3.1]* explains how subject limb surface area will be calculated, but does not describe the procedure by which it will be measured, or how the location of the centers of the four circumferences will be recorded to enable later placement of the dosimeters at the same location.

No data collection form for the field repellency phase is included in the protocol.

(b) What steps are proposed to ensure measurements are accurate and reliable?

- Alternate subjects will be enrolled to ensure adequate sample size

- Subjects will be trained to handle ticks and to remove them before they can bite
- All crossings and repulsions are verified and recorded by a research technician

(c) What QA methods are proposed?

"A separate, professional Quality Assurance Unit (QAU) will inspect the study. The QAU will report to the Study Director. Protocol Review and Comments must take place before data collection commences. In-Life Inspection must include observing the measurement and recording of key variables by subjects and researchers. In addition, the Final Report will be audited for completeness and accuracy. A QAU Statement will address compliance and noncompliance or any omissions in auditing. Findings from the In-Life Inspection and the Final Report, as well as the QAU Statement, will be transmitted to both the Study Director and to the Sponsor Monitor." (p. 39)

Reports of QAU findings should also be incorporated into the final report.

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

"Mean CPT will be calculated across all 10 subjects per treatment, and will be presented with standard deviation and 95% confidence interval." (p. 30)

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern? How was it identified?

The population of ultimate concern consists of people who would purchase and use tick repellents. Little information is available to characterize this population, but it is presumed that repellent users are highly diverse in age, gender, physical size, general health, attractiveness to questing ticks, and other characteristics. The population from which subjects are recruited appears to be chosen largely on the basis of convenience, and is not screened for past or likely future use of repellents.

(b) From what populations will subjects be recruited?

"For reasons of practicality and control, we work with people from the community in which our business is located: Davis, CA. Davis is a university-dominated community, and so the population demography differs somewhat from non-university communities. Based on census data, the four major race/ethnicity groupings in the local population are: 70% Caucasian, 15% Asian, 8% Hispanic, and 2% African-American (these are approximate numbers).

"Initial contact is through word-of-mouth and telephone contact with subjects who have participated in similar previous Carroll-Loye repellent efficacy tests and have agreed or requested to be in our Volunteer Database. At present, that database consists of 30 males and 28 females. Of the 58 total subjects, 44 (76%) identify themselves as Caucasian, 8 (14%) as Asian, 3.5 (6%) as Hispanic (white), and 2.5 (4%) as African American. These proportions match the city's racial distribution quite closely.

"75% of the subjects are range in age from 20 to 40; the remainder are between 40 and 55. Educational levels are as follows: 7 with a Ph.D., 8 with an M.S., 18 currently in graduate programs, 14 with a B.S. or B.A., and 10 undergraduate students. Among those who are not students, there are 15 professional researchers, 5 professional artists, 3 teachers, 3 office workers, 2 business owners, 2 sales people, 1 professor, 1 massage therapist, and a few whose professions are unspecified. The age distribution, skewed toward youth, reflects the collegiate community. Education levels are very high for the same reason. Profession is heavily slanted toward life sciences researchers and students, reflecting the community and the nature of the studies. While many of the subjects with whom we work show a keen and enduring interest in participating, such interest is not likely predictive of anything atypical about the results stemming from their presence in a study.

"Compared to the US population (potential repellent users), our sampling frame tends to under-represent blacks and over-represent Asians. It is also younger and better educated. Based on review of the scientific literature regarding individual differences in repellent performance and attractiveness to ticks, we conclude that those deviations from the ideal frame will not influence the results' representativeness, or their generalizability to the greater population. Lastly, because our Volunteer Database cohort is comprised by individuals who regularly spend time in outdoor setting (and thereby may have relatively frequent encounters with biting arthropods), this group is probably appropriate for insect repellent users in general." (pp. 18-19)

(c) Are expected participants representative of the population of concern? If not, why not?

By excluding children, pregnant or lactating women, non-English speakers, and those in poor physical condition, among others, the exclusion criteria will mean that participants will not be representative of at least some segments of the population of concern.

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

Inclusion: age 18-55, written consent, speak and read English. (p. 13)

Exclusion: phobic of ticks; sensitivity to any product ingredients; poor physical condition; unwillingness to submit to brief query about personal condition; use of insect repellent within one day before study; unwillingness to abstain from alcohol, smoking, and perfumed products the night before and during the testing; pregnant or lactating; inability to apply test materials; inability to see nymphal ticks on skin; student or employee of Study Director. (pp. 13-14)

In general, these criteria for inclusion and exclusion appear appropriate.

(b) What, if any, is the relationship between the investigator and the subjects?

Subjects are recruited from "the community in which [the Investigator's] business is located . . . . Initial contact is through word-of-mouth and telephone contact with subjects who have participated in previous Carroll-Loye repellent efficacy tests and have agreed or requested to be in our Volunteer Database." (p. 18)

"Our Volunteer Database has grown through people who . . . learn of our work from persons who have worked with us; we do not direct or actively encourage that process. In those initial contacts, the prospective subjects typically have prior knowledge of our work and its general purpose, and what their fellows have experienced in prior studies. . . . About half of our subjects are present or past University of California, Davis . . . students . . . in life science programs. Students who depend on the Principal Investigator for employment or for scholastic purposes are not eligible to participate." (p. 19)

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

No subjects from a vulnerable population are proposed.

(d) What process is proposed for recruiting and informing potential subjects?

The recruiting/informing process to be used is extensively described in the protocol on pp. 20-21 and in the informed consent document.

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

"Students who depend on the Principal Investigator for employment or for scholastic purposes are not eligible to participate." (p. 19)

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

"[E]ach research study participant will receive a cash payment of $20 per hour. . . . If you are designated as an 'alternate subject' you will be paid for the hours you spent being trained, plus you will receive a payment of $50 to compensate for being inconvenienced." (p. 44)

A subject who participated in both the dosimetry phase (2-2.5 h) and repellency testing for one formulation (8-14 h) would be compensated at $200-$330. A subject who participated in the dosimetry phase and repellency testing for all three formulations would be compensated at $520-$890.

(b) Is proposed remuneration so high as to be an undue inducement?

No.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?

No.

(d) How and when would subjects be paid?

"Payment will be made at the end of each visit or whenever you withdraw from the study." (p. 44)

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?

The results of prerequisite hazard studies are not reported. The spray materials are currently registered by EPA; the lotion material is the subject of a pending application for registration.

(b) What is the nature of the risks to subjects of the proposed research?

"The study-associated risks are of three types: exposure to test materials, exposure to biting arthropods and possible exposure to arthropod-borne diseases." (p. 5)

"The repellent's active ingredient has a low acute and chronic risk profile, a fact established through experimentation and through a history of consumer use. The concentrations of the active ingredient in the products being tested are similar to those of other Picaridin products which EPA has recently registered." (pp. 5-6) The

consent document informs subjects that "the repellents will irritate the eyes on contact, and is harmful if swallowed", and "there may be some unknown or infrequent and unforeseeable risks associated with using this product, including allergic reaction or interaction with a medication." (p. 43)

"While no bites are expected, . . . the testing will be conducted with laboratory ticks reared on quarantined rodents . . . screened to be pathogen-free for all tick-transmitted pathogens and hantavirus using appropriate culture, direct detection (PCR), and immunological screening assays." (p. 6) Subjects are informed that "measures will be implemented to make sure that ticks are removed before they have an opportunity to bury in the skin." (p. 43)

The risks of tick bites and of exposure to tick-borne disease, mentioned in the protocol, are not addressed in the consent document. The measures to be implemented to ensure ticks don't bury and bite, and by whom they would be implemented, are not explained. Both these deficiencies should be corrected.

Both the protocol and the consent document are silent with respect to risks of embarrassment or other psychological risks associated with the requirement for pregnancy testing of female candidates, although the research design effectively minimizes these risks.

(c) What is the probability of each risk associated with the research? How was this probability estimated?

No numerical probability is estimated. "In summary, the relatively benign quality of the repellents and the technical precautions we employ indicate that the chance that any subject will be at a health or safety risk is extremely small." (p. 6)

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

- Candidates known to be phobic of ticks are excluded.
- Candidates with known sensitivity to the test repellents or any of their ingredients are excluded.
- Subjects will be trained to handle ticks and observe their behavior (p. 56) and to remove ticks from their arms before they have time to bury and bite.
- Ticks will be lab-reared and pathogen-free.
- Experienced technical personnel will be present at all times to assist.
- First Aid materials will be available on-site
- No control with formulation matrix exclusive of active repellent ingredients.
- A physician who aware of the study will be on call on the day of testing.
- Results of pregnancy testing will be handled with discretion, and recruitment of alternate subjects permits withdrawal without explanation.

(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?

Actual dose levels will only be established by the results of the first, dosimetry phase of the proposed study. The dosimetry phase is intended to establish a "typical consumer dose".

Actual dose rates are unlikely to exceed 1 g/600 cm^2 skin area. At an estimated dose rate of 1 g/600 cm^2, each treated subject will receive a dose of about 1000 mg of repellent. The concentration of the test materials is 7% or 15%, equivalent to 70 or 150 mg picaridin. Because of the ethanol in the spray formulations this figure is adjusted by an "ethanol enhancement" factor of 2.26, yielding an adjusted dose of 152 mg (2.3 mg/kg for a 70 kg adult) for the 7% formulation or 339 mg (4.8 mg/kg for a 70 kg adult) for the 15% spray. No ethanol enhancement factor is needed for the 15% lotion, so 150 mg picaridin would be equivalent to 2.1 mg/kg for a 70 kg adult. The NOAEL for acute dermal toxicity in the rat for picaridin is 5000 mg/kg body-weight, picaridin is less readily absorbed by human skin than by rat skin, and we do not expect the inert ingredients other than ethanol to affect the systemic dermal toxicity. Thus the estimated margin of exposure for picaridin acute dermal toxicity for the 15% spray containing ethanol is not less than and may be substantially greater than 5000/4.8 or 1,042. The margin of exposure for the 7% spray and for the 15% lotion would be higher.

(c) What stopping rules are proposed in the protocol?

"If at any time during the study a subject suffers a skin reaction or feels ill, he or she is instructed to inform the Study Director . . . . Such subjects will be immediately withdrawn from testing and medical management will be implemented." (p. 6)

"Subjects are directed to cease tick exposures when a crossing is followed by another crossing within one-half hour, i.e., in either of the subsequent two exposure periods." (p. 27)

(d) How does the protocol provide for medical management of potential illness or injury to subjects?

"If you are injured as a result of being in this study, a consulting physician who is aware of the study will be contacted immediately by telephone. Medical treatment will be available from a health care facility." (p. 43)

(e) How does the protocol provide for safety monitoring?

"Technical personnel will monitor, and subjects will self-monitor, for allergic and irritant skin reactions, particularly redness, edema, itching or pain, and report any such reactions to the onsite technical personnel. Any subject showing adverse skin reactions will immediately stop participating. The treated skin will be gently washed

with clean water and mild soap to remove the test product, and the area will be gently dried with a clean towel. The subject will cease further exposures to ticks.

"On the testing day, a physician who has read the protocol and discussed the research with the Study Director will be on call. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will call 911 by cellular or satellite telephone and cooperate as instructed with emergency personnel. . . .

"As part of Medical Management, the Study Director will record all benign and adverse health observations." (pp. 22-23)

(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

"All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash . . . within 48 hours of the conclusion of the test day, or at any time should they have health concerns relating to their participation in the efficacy testing." (p. 23)

While subjects may indeed be asked to do this, the Informed Consent Document is silent on this point.

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

"Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party. If necessary, Carroll-Loye Biological Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study." (pp. 43-44)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

"There are no immediate benefits to you from your participation." (p. 44)

(b) What benefits to society are anticipated from the information likely to be gained through the research?

"Balanced against these slight risks are substantial and reasonably likely benefits. The principal beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current U.S. EPA registration standards. . . . Arthropod-borne disease is of growing significance in the U.S. and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities. A test such as the one proposed here is the Sponsor's only legitimate path toward further

product development and greater availability of new Picaridin-based tick repellents to U.S. consumers." (pp. 6-7)

"[B]y serving as a participant you may assist in making new insect repellent products available to consumers." (p. 44)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

"The principal beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current U.S. EPA registration standards." (p. 6) Assuming eventual regulatory approval, indirect beneficiaries would include those repellent users who prefer these formulations to other available repellents.

(d) What is the likelihood that each identified societal benefits would be realized?

The testing is likely to demonstrate that the formulations are effective in repelling ticks, and thus the sponsor is likely to realize a direct benefit from the research. Realization of other societal benefits will depend on consumer acceptance of the formulations.

6. Risk/Benefit Balance

(a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

The protocol systematically reduces risks to subjects without reducing the robustness of the scientific design. No reasonable opportunities to further reduce subject risk have been overlooked. The resulting residual risk to subjects is very low. The potential benefits to repellent users from availability of a wider variety of effective repellents are likely to be realized, and make the residual risks to subjects in this proposed research reasonable.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Plantation FL

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? If so, by whom?

Not reported. IIRB is not listed as accredited on the AAHRPP website.

(e) Does this IRB hold a Federal-Wide Assurance from OHRP?

Not reported. IIRB is not listed as holding an FWA on the OHRP website.

(d) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

The transmittal of the protocol, "site questionnaire", and related materials to the IIRB and related correspondence, including the IIRB notification of approval (pp. 36-37) are provided. Minutes of the IIRB meeting at which this protocol was discussed were submitted to EPA directly by the IRB. These minutes report approval of the protocol version of 7/10/07 (pp. 3-35), the Site Questionnaire (pp 63-66), and the Administrative Letter dated 7/17/07 (p. 67). The minutes further report that the IIRB approved the consent document as submitted.

Documentation of IIRB procedures meeting the requirements of 40 CFR 26.1125 has previously been submitted directly to EPA. In a July 26 e-mail transmitting the minutes to EPA, IIRB's Director of Operations asserted that there have been no subsequent changes to the IIRB's procedures.

(e) What standard(s) of ethical conduct would govern the work?

"U.S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA §12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710)." (p. 7)

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject? Yes.

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117? Yes.

(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research? Yes.

(d) What is the literacy rate in English or other languages among the intended research subjects?

100%. English literacy is a requirement for participation.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects? n/a

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

Frequent opportunities to ask questions.

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

See protocol pp. 19-21 and consent form (pp. 39-45)

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Candidates are offered repeated opportunities to decide not to participate; participants are offered repeated opportunities to withdraw. Exclusion factors rule out participation by employees or students of the Study Director. Recruitment of alternate subjects reduces the likelihood that subjects might be reluctant to withdraw lest their withdrawal might compromise the validity of the investigation.

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

Subjects are identified by name and by number. Only the number is used on data collection forms provided (pp. 46-50). Recruitment of alternate subjects provides an opportunity for discrete withdrawal without explanation. Subjects are told they "may access [their] own records by contacting the Study Director," and that they will not be identified in any published reports of the study. (pp. 44-45)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

Subjects are so informed in the recruitment interview (pp. 19-21) and in the consent form.

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

Subjects who decide not to participate will simply go their way. Subjects identified as alternates, and any who withdraw from the research, will be paid for their time (p. 44).

§ 26.1111 Criteria for IRB approval of research
Protocol SPC-002

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	N/A	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	N/A	

§26.1116 General requirements for informed consent
Protocol SPC-002

Criterion		Y/N	Comment/Page Reference
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 or the subject's legally authorized representative		Y	All subjects will provide legally effective informed consent.
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		Y	The procedure described in §9.1.5.3 provides sufficient opportunity to consider . . . and minimizes the possibility of coercion or undue influence.
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		Y	Information is clearly presented in plain English
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence		Y	The IC contains no exculpatory language
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Y	p. 39
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	p. 43
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	p. 44
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	Y	p. 44
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	pp. 44-45
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Y	Compensation p. 44 Medical Treatment pp. 43-44
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Y	p. 44
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Y	p. 45
(b) When appropriate, one or more of the following elements of information shall also be	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	Y	p. 43
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	p. 45
	(3) Any additional costs to the subject that may result from participation in the research	Y	p. 44
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	N/A	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	Y	p. 43
	(6) The approximate number of subjects involved in the study	Y	p. 40
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		Y	p. 39

§26.1117 Documentation of informed consent
Protocol SPC-002

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	Y	Consent form pp. 39-45 Procedure pp. 20-21
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	Y	Consent form meets requirements of §26.1116; procedure described in protocol §9.1.5.3 provides adequate opportunity to read it before it is signed.
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	N/A	

40 CFR 26.1125 Submission of proposed human research for EPA review
Carroll-Loye SPC-002 (Version of 6/10/2007)

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement		Y/N	Comments/Page Refs
The following Information, to the Extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 5-6, 43
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 6, 13-14, , 10-11, 13, 15-17, 23-24, 26-27
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	pp. 7, 44
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 5
		(5) The balance of risks and benefits of the proposed research.	Y	pp. 6-7
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	pp. 39-45 (approved as submitted)
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 18-19. No advertisements used
	§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	pp. 20-21
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 36-37, 63-70
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 36-37
all information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.		Y n/a Y n/a	pp. 3-35; 39-67 None accompanied the proposal p. 39-45 Initial review of new proposal
	(2) Minutes of IRB meetings . . . 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 Y Y n/a n/a	 IRB minutes; separate document IRB minutes IRB minutes No changes required No controverted issues
	(3) Records of continuing review activities.		n/a	n/a for protocols
	(4) Copies of all correspondence between the IRB and the investigators.		Y	Provided by investigator pp. 36-37, 63-70
	(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 Y	On file with EPA
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		N	On file with EPA (Claimed CBI)
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols