UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

October 1, 2010

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

FROM: Clara Fuentes, Ph.D., Efficacy Reviewer
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TO: Linda Hollis, Chief, Biochemicals Pesticide Branch
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REF: Carroll, S. (2010) Field Efficacy Test of PMD and Lemongrass Oil-Based Repellent 'No Mas' Against Mosquitoes. Efficacy Test Protocol No Mas 003. Unpublished document prepared by Carroll-Loye Biological Research. 340 p.

We have reviewed the referenced protocol for a field test of mosquito repellency from both scientific and ethics perspectives. This review assesses the scientific aspects of the proposed research in terms of the recommendations of the final test guideline for Product Performance of Skin-applied Insect Repellents of Insect and Other Arthropods Test Guidelines (OPPTS Test Guideline No. 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. 4-32) and the associated consent documents as approved by the Independent Investigational Review Board, Inc. (IIRB) (pp. 33-62), the following supporting documents were considered in this review:

- IIRB Approval letter of 7/20/10 (pp. 335-336)
- Data recording forms (pp. 63-76)
- Subject training materials for mosquito handling (pp. 77-79)
- Draft label for product and MSDSs for active ingredients (pp. 81-94)
- HSR Training records for investigators (pp. 182-183)
- Index of CLBR-IIRB Correspondence (pp. 194-195)
- CLBR-IIRB Correspondence (pp. 196-340)

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 mosquitoes of a lotion formulation containing 16% para-menthane-3,8-diol (PMD) and 2% lemongrass oil, delivered from a squeeze bottle. EPA requires efficacy testing of this specific formulation to support U.S. registration of the product. Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid insect bites, cannot readily assess the efficacy of a product independent of EPA's approval.

2. **Subject Selection:** Subjects will be recruited from Carroll-Loye Biological Research's (CLBR's) "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 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. Since students and employees of the study director and employees of the sponsor will be excluded as possible subjects, there are appropriate protections in place to ensure that none of the subjects are likely to be subject to coercion or undue influence over their decision to participate in the research.

3. **Risks to Subjects:** The protocol and consent forms discuss risks of five kinds: risks from exposure to the test material; risks of exposure to biting arthropods; risks from exposure to disease vectors; risks of physical stress in the test environment; and risks of stress from learning the results of a pregnancy test. All practical steps to minimize subject risks have been taken.

   Based on the acute toxicity testing submitted and reviewed by EPA, the test material is accurately characterized in the informed consent form as a moderate eye irritant and possible skin irritant.

   Because of the generally low acute and chronic hazard profile of the test material, the design of the research to minimize exposure, and the training of subjects to remove mosquitoes before they bite, the probability of occurrence of the identified hazards is accurately characterized as "extremely small."

4. **Benefits:** There are no direct benefits to subjects. This is made clear in the protocol and informed consent form. If the testing shows good efficacy, the direct beneficiary of the research is likely to be the sponsor.

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 reasonable in light of the potential benefits of the data to future repellent users.

6. **Independent Ethics Review:** The Independent Investigational Review Board, Inc. (IIRB), of Plantation, Florida, has reviewed and approved the protocol and informed consent materials. IIRB is independent of the investigators and sponsors. Satisfactory documentation of IIRB procedures and membership is on file with the Agency.

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

8. **Respect for Subjects**: Methods proposed for managing information about prospective and enrolled subjects are adequate to protect their privacy. Subject names and other personal information are linked on only one form to their arbitrary "subject number"; in all other data collection forms subjects are identified only by their assigned number.

   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.

The protocol should be revised before study execution to exclude as permissible subjects employees of the study sponsor.

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 field conditions of a new mosquito repellent lotion containing 16% plant derived p-menthane-3,8-diol (PMD) and 2% lemongrass oil (citral). The main objective of the study is to quantify the efficacy of the formulation to repel mosquitoes in the field. The protocol's objective is to determine the duration of efficacy of the lotion formulation in repelling three mosquito species (*Culex, Anopheles,* and *Aedes)* when applied at a typical consumer dose. The endpoint will be the time of repellent failure expressed as the time of First Confirmed Landing with Intent to Bite (FCLIBe) for each subject. Efficacy is expressed for each subject as Complete Protection Time (CPT), which is the period from application of the repellent until time of FCLIBe, or conclusion of the test, whichever occurs first. Mosquito specimens will be collected from treated and untreated subjects and taken to the laboratory for identification, using taxonomic keys and stereomicroscopy. Disease vectors will be screened for transmissible viruses, and any positive results will be provided to the appropriate test subject(s).

1. **Study design:**

The duration of efficacy of the test material will be evaluated in the field with ten treated subjects, five of each sex, at each of two sites representing distinct ecological habitats. Three additional subjects will be enrolled as alternates to replace any subjects who may withdraw prematurely from the test, or who may fail to show up for testing. Untreated subjects will monitor activity at the test sites throughout the duration of the test by exposing either their lower leg or forearm for periods of 1 minute every 15 minutes. Minimum acceptable ambient biting pressure is defined as 1 landing with intent to bite (LIBe) per minute. Untreated subjects will not be compared to treated subjects.

2. **Statistical design:**

The aim of the research is to characterize the duration of repellency defined as Complete Protection Time (CPT). The mean of ten individual subject values will be used to estimate a central measurement of CPT at each test site. The protocol characterizes ten subjects as a compromise between ethical and economic considerations, based on the rationale that ten subjects are two-thirds more than the historical EPA requirement of six subjects. Furthermore, if few values are censored, and particularly, if the range of values is not great, a sample size of ten should give excellent estimates of mean, median, and variation around those values, relative to historical standards.

While EPA has recently accepted repellent efficacy data based on a sample size of ten, EPA recommends that the investigator revise and expand the explanation offered for the proposed sample size. EPA thinks that reference to historical standards is irrelevant in light of current guidelines and should be deleted. EPA's guidelines (OPPTS Test Guideline No. 810.3700) provide: "(v) Sample size. The sample should be large enough to be likely to yield a definitive answer to the research question being addressed, and its size should be justified statistically in each protocol, taking into account the specific characteristics of the proposed research and the desired accuracy and precision of the results. Researchers are encouraged to consult a statistician to help determine appropriate sample size." Therefore, investigator should revise the rationale in the protocol to include a statistical justification for the proposed sample size in light of the desired accuracy and precision of the results.

3. **How and to what will human subjects be exposed?**

Subjects will be exposed to test material and mosquitoes in the field. Each subject will be treated on one forearm or lower leg, depending of feeding behavior of predominant mosquito species active in the field. A standardized typical dose, expressed as volume per unit area, will be scaled to the measured surface area of each subject's forearm or lower leg, and applied by technicians using tuberculin (1 ml) syringes. The test material has been tested in animals for acute toxicity. The NOAEL for acute dermal LD_{50} of No Mas is greater than 5,000 mg/kg body weight. Thus, exposure of 14.3 mg/kg of lotion, containing 18.0% of combined active ingredients, results in an estimated MOE > 100. Most inert ingredients in the formulation are classified by the Agency as relative safe for all uses and have a low acute and chronic risk

profile. Only a few ingredients present ocular and dermal irritation potential; other ingredients are commonly used in drugs and cosmetic products. Subjects with known allergic reactions or other skin conditions are excluded from participation in the test. Data from animals studies show that the formulation is of low toxicity by oral and dermal routes of exposure. It is not irritating to the skin, and it is not a skin sensitizer.

Results from toxicity testing:

- Primary eye irritation study on rabbits shows that the No Mas is a moderate irritant to the eyes.
- Dermal sensitization study in Guinea pigs (Buehler method) shows that the test material is not a contact sensitizer.
- Primary skin irritation in rabbits study shows that No Mas is moderately irritating to the skin.
- The single dose acute dermal LD_{50} of the formulation is >5,000 mg/kg in male and female rats.
- The acute oral LD_{50} of No Mas is >5,000 mg/kg in male and female rats

Subjects will be exposed to naturally occurring populations of mosquitoes in field sites where tests are being conducted and mosquito-borne pathogens have not been detected by PCR-based screening of trapped mosquitoes for at least 2 weeks. Subjects with known allergic reactions to mosquito bites will be excluded from research participation.

4. Endpoints and Measures:

A standard "typical consumer dose" will be determined in the dose determination phase, and used for each subject in the repellency phase. The end point of the dose determination phase will be a standard volumetric rate of application expressed in ml/cm^2.

In the repellency phase, efficacy will be measured as Complete Protection Time (CPT) for each subject, defined as the time between application of test material and the First Confirmed Landing with Intent to Bite (FCLIBe). A Landing with Intent to Bite (LIBe) occurs when a mosquito alights on treated skin and extends its proboscis to the skin while ceasing locomotion. First Confirmed LIBe (FCLIBe) is defined as a LIBe followed by another LIBe within 30 minutes. The end point will be the time of repellent failure expressed as the time of the FCLIBe for each subject. Repellency will be expressed as average CPT, which is measured as the mean time across subjects from initial application of a typical consumer dose to the time of FCLIBe.

E. Compliance with Applicable Scientific Standards

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

- Prerequisite acute toxicity research to characterize toxicological profile of the formulation and calculate margin of exposure (MOE).
- Dosimetry
- Experimental design
- Pre-training of subjects on how to handle mosquitoes.

The following elements in the protocol require revision before the research goes forward:

- The statistical analysis plan should discuss how non-normally distributed data points will be treated. That is, how the researcher plans to analyze and interpret results from non-normally distributed data points that may follow an unknown distribution.

- On page 28, line 41, delete the phrase "for each test material" because this protocol is for testing one single formulation.

- The sequential exposure table on page 74 should include 80 sequential exposure intervals. It is not clear why only 36 counts are tabulated, and how the 44 remaining intervals can be accommodate one single column, labeled as "etc." If the test is going to last more than 9 hours, a second page will be needed.

Attachments:

1. Summary Review of Protocol NO-MAS 003 dated 7/15/2010
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: NO-MAS 003

Title: Field Efficacy Test of PMD and Lemongrass Oil-Based Repellent 'No Mas' Against Mosquitoes.

Date: July 15, 2010

Principal Investigator and any sub-investigators:

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1. Societal Value of Proposed Research

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

The objective of the dosimetry phase "is to determine the amount of repellent a consumer might typically apply using each of the delivery systems in the study, and to determine the dosage to be applied during the repellency phase of the study. The endpoint will be a standard rate of application expressed in ml/cm^2." (p. 4)

The objective of the repellency phase is to determine the duration and efficacy of the test Material(s) in repelling three species of mosquitoes (*Culex, Anopheles, and Aedes)* when applied at a typical consumer dose. (p. 4)

"Efficacy and duration will be measured as Complete Protection Time, or CPT, defined herein as the time between application of test material and the First Confirmed Probing called 'Landing with Intent to Bite', or 'LIBe', which is defined as when a mosquito alights on the treated test skin of a subject and extends its proboscis to the skin surface

while ceasing locomotion. A 'First Confirmed LIBe' is that which is followed by another within 30 minutes." (p. 4)

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

"The US Centers for Disease Control (CDC) has acknowledged the existence of substantial consumer interest in new and effective insect repellent products, including the choice of a variety of formulations, delivery systems, and concentrations of active ingredient. US EPA has requested new, US-based efficacy data as a condition of registration for the test material(s). The rationale for this study is to provide those efficacy data. The information will also be used in product labeling and for increased user acceptance." (p. 5)

(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 material.

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

EPA requires product-specific efficacy data to support its registration. No previous testing of this product against mosquitoes under proposed used pattern has been conducted.

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

"Human subjects are required because they represent the target system for the test material, and sufficiently reliable models for repellency testing have not been developed." (page 5: line 14 - 16).

2. Study Design

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

The main objective of the study is to quantify the lasting efficacy of the formulation to repel mosquitoes in the field. The specific protocol's objective is to determine the duration of efficacy of the lotion formulation in repelling three mosquito species (*Culex, Anopheles,* and *Aedes)* when applied at a typical consumer dose under field conditions.

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

The objective cited may be achieved by the study as proposed if the protocol is revised and amended to explain, in more detail, the following:

- How will these data be summarized, analyzed and interpreted if the results show that the data points are not normally distributed and the data follows an unknown distribution?
- What measurements will be taken to minimize right censoring?
- How does the researcher plan to minimize, and account for variability in the experiment?

2.1 Statistical Design

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

The rationale for this sample size appears on pp. 18 to 20 (§ 4.1) of the study protocol. Researcher's justification for sample size is based on the argument that a 10 subjects sample reflects a compromise between cost and precision; ten subjects are two-thirds more than the historical EPA requirement of 6 subjects. In Addition, it is stated in the study protocol, page 19: lines 30 -33, that "If a minority of values is censored, and particularly if the range of values is not great, a sample size of 10 should give an excellent estimates of mean, median, and variation around those values, relative to historical standards."

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

There are no comparison materials or positive controls. Omission of matrix and comparison materials is appropriate for the study design. No direct comparisons of treated and untreated subjects are contemplated in the statistical analysis plan.

(c) How is the study blinded?

n/a. There is one treatment only.

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

All subjects will be assigned to the treated group, which will be stratified by gender. Table 8 on page 24 summarizes the proposed distribution of test material among subjects. The treatments will be balanced between arms and legs if both limbs are used, depending on the feeding behavior of mosquitoes present in the field. Two untreated subjects are also shown in table 8. Their untreated skin will be balanced between arms and legs similarly to treated subjects.

(e) Can the data be statistically analyzed?

Yes. The application rate for efficacy testing will be an average typical consumer dose estimated from dosimetry analysis (§ 4.6) developed by CLBR laboratory. Subjects' dose means based on 3 applications per subject will be used to calculate dose grand mean (± SD) across all 10 subjects. In the efficacy phase, 10 individual subject values for CPT will be obtained and analyzed. CPT will be measured as a single time value per subject. Mean CPT will be calculated across all 10 subjects, with standard deviation and 95% confidence interval (page 29: lines 22 to 27). Kaplan-Meier survival analysis will be employed to accommodate some data censoring. The Kaplan-Meier test will be also employed to estimate the median CPT, and the time until 25% efficacy failure of the test material. In the presence of high censoring frequency, median and mean values will be underestimated. Ambient landing pressure will be measured as number of landings per untreated subject per exposure period and span of exposure (page 29).

(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)

"In the efficacy phase, CPT, defined as period between application of formulation and FCLIBe or end of test, will be measured as a single time value for each subject. A mean CPT will be calculated across all 10 subjects, and will be presented with standard deviation and 95% confidence interval. Data will be normalized as possible to enhance the value of confidence interval calculations." (p. 29).

"To examine the temporal pattern of failure further, we will employ Kaplan-Meier survival analysis by subject. Kaplan-Meier survival analysis accommodates some data censoring in the event that any subjects withdraw or are withdrawn before failure. In addition, we will estimate the Kaplan-Meier median, and the time until 25% failure, for each test product. In the presence of a high frequency of censoring, median (and mean) values will be underestimated." (p.29)

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

The proposed statistical methods are based on assumption of normality, low frequency of right censoring, and historical standards. The researcher should elaborate on the appropriate methodology to meet such assumptions, and provide scientifically- based rationale for anticipating that those assumptions will be met.

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

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

increase in sample size from six to ten subjects will improve precision and is consistent with suggestions from HSRB to EPA (pp. 29 – 30). Historical standards are irrelevant in light of EPA current guidelines (OPPTS Test Guideline No. 810.3700). A sample size of 10 may be adequate depending on experimental variability, experimental design and interpretation of test results.

2.2 How and to what will human subjects be exposed?

Subjects will be exposed to test material and mosquitoes in the field. A standardized typical dose, expressed as volume per unit area, will be scaled to the measured surface area of each subject's forearm or lower leg and applied by technicians using tuberculin (1 ml) syringes. The repellent's active ingredients have a low acute and chronic risk profile (§2) (page 5: lines 40 to page 5: lines 1 to 21), and the inert ingredients are classified by the Agency as safe for use. Only a few ingredients of the inert ingredients present ocular and dermal irritation potential. The other ingredients are commonly used in drugs and cosmetic products. The test material has been tested in animals for acute toxicity. Subjects with known allergic reactions (§3.3.3 and §3.3.5), or other skin conditions (§3.3.4) are excluded from participation in the test.

Subjects will be exposed to naturally occurring populations of mosquitoes in field sites where tests are being conducted and mosquito borne pathogens have not been detected for at least 2 weeks (§1.3.2; page 7: lines 23 to page 8: 10). Subjects with known allergic reactions to mosquito bites will be excluded from research participation ((§3.3.3).

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

Efficacy data to support label claims for this product are required by EPA as a condition of registration. EPA requires submission of efficacy data for all products claiming efficacy against human health pests.

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

Dosimetry is the procedure employed in this study to estimate the standard consumer dose used for testing efficacy.

(c) What duration of exposure is proposed?

The repellency phase will last from 12 to 18 hours; the period of actual exposure is uncertain; it may be less than 8 hours (excluding travel time) to as long as 18 hours, depending on how long the repellent remains effective (page 3 in Informed Consent Authorization to Participate as a Research Study Subjects). Data sheets for Mosquito LIBes at 15 Minutes Intervals show 80 data points, which corresponds to 20 hours of observations. Although not specified, the reviewer assumes that the total hours of observations will be equally divided between the 2 testing sites, and it will be 10 hours of total observations per site. That assumption needs to be verified by the researcher.

2.3 Endpoints and Measures

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

"Subject measurements" include subjects' limbs surface area, which may be measured or based on historical subject data as explained. "This data will be kept on file for each subject. Subjects will be re-measured biennially or if, when asked, they indicate they may have gained or lost weight or muscle mass on their limbs since their measurements were last taken." (page 21: lines 1 – 10). Volume of test material delivered to the skin is described in §4.7. (p. 23). These measurements are appropriate to estimate the standard consumer dose employed for efficacy evaluation.

Endpoints for efficacy evaluation (page 29: lines 8 – 14):

- Exposure delay (min)-time between application and first exposure
- Minutes to FCLIBe.
- Complete Protection Time (CPT)–time between application and FCLIBe or end of test.
- Total number of landing mosquitoes per minute on untreated subjects at the beginning of each interval.

Data forms are presented for dosimetry (limbs' measurements on page 64; grams of applied product on page 65; randomized treatment allocation on page 66, and repellent applications on page 67); Field Environmental conditions on page 68; Researcher Notes on page 69, and Mosquito LIBes at 15 minutes intervals on pages 70 – 73 (these data sheets include 80 exposures of one minute each at 15 minutes intervals per subject); one data sheet for 36 Sequential Exposure Intervals up to "etc" on page 74; Research Subject Tracking form on page 76, and data sheet for Pools of Mosquito Species submitted to UCD by CLBR on page 75. The sequential exposure table on page 74 should include 80 sequential exposure intervals. It is not clear why it stops at 36 counts, and how the 44 remaining intervals would be accommodated under one column labeled as "etc."

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

- Test material will be applied by laboratory technicians.
- Alternate subjects will be enrolled to ensure adequate sample size.
- Subjects will be trained to handle mosquitoes and to remove them before they can bite.
- All landings 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 of Operations. 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 technicians. 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 QUA statement will be transmitted to both, the study director and to the sponsor Monitor." (p. 30).

(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.29)

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 mosquito 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 mosquitoes, 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 associated with 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. Compared to the Population of Concern (the US population - all potential repellent users), our sampling frame tends to under-represent blacks and over-represent Asians. It is also young, well educated, and slanted towards life science researchers and students.

"Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers. The size and composition of the database varies over time as new individuals volunteer and old volunteers move out of the Davis area, but is now typically over 100 individuals, with the following average ethnic (self-identified) and gender distribution (averaged over 3 years):

Male	52%
Female	48%
Caucasian	73% [72% on IIRB Site Questionnaire Form]
Asian	12%
Hispanic	8%
African-American	3%
Middle Eastern	5%

"In general, about three-quarters of the subjects are age 20-40, with the remainder between 40 and 55. Final composition is not determined until enrollment is completed. The relevant demographics of the participants will be reported." (p. 12)

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

"Based on review of the scientific literature regarding individual differences in repellent performance and attractiveness to mosquitoes, we conclude that this study's deviations from the ideal frame will not influence the representativeness of the results, 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. 13-14)

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, because the study will be replicated twice at 2 different mosquitoes habitats.

3.2 Equitable Selection of Subjects

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

"Inclusion:

1. Age 18-55;
2. Written consent; and
3. Speak and read English.

Exclusion:

1. Known to be hypersensitive to mosquito bites;
2. Phobic of biting insects or insect bites;
3. Known to be allergic to insect repellents or common cosmetics;
4. Known to be sensitive to any of the test material ingredients;
5. Poor physical condition;
6. Unwilling to submit to brief query about personal condition;
7. Use of insect repellent within one day proceeding the efficacy test;
8. Unwilling to refrain from use of perfumed products, alcoholic beverages or smoking after 9 pm the evening preceding the efficacy test and throughout that test;
9. Known to be pregnant or lactating;
10. Unable to deliver the test material to own left and right limbs for dosimetry;
11. Unable to see biting insects on skin or otherwise effectively monitor and remove biting insects that contact skin;
12. Student or employee of Study Director; and
13. Does not regularly spend time in outdoor settings." (page 14-15)

Exclusion factor #12 should be revised to exclude employees of the sponsor, as well as students or employees of the study director.

(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 . . . . Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers." (page 12)

Students and employees of the Study Director are excluded from participation. (page 15)

(c) If any potential subjects are likely to be especially vulnerable to coercion or undue influence, what is the justification for including them?

None of the subjects are expected to be especially vulnerable to coercion or undue influence.

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

The recruiting/informing process to be used is described in the protocol on pp. 14-17.

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

Students and employees of the Study Director are excluded from participation. (p. 15) No eligible subjects are potentially subject to coercion or undue influence.

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." (page 41)

(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." (page 41)

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 material?

Acute toxicity studies required for the registration of an insecticide were conducted on animals. Data from animals studies show that the formulation is of low toxicity by oral and dermal routes of exposure. It is not irritating to the skin, and it is not a skin sensitizer.

Results from toxicity testing:

- Primary eye irritation study on rabbits shows that the No Mas is a moderate irritant to the eyes.
- Dermal sensitization study in Guinea pigs (Buehler method) shows that the test material is not a contact sensitizer.
- Primary skin irritation in rabbits study shows that No Mas is moderately irritating to the skin.
- The single dose acute dermal LD_{50} of the formulation is >5,000 mg/kg in male and female rats.
- The acute oral LD_{50} of No Mas is >5,000 mg/kg in male and female rats.

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

The protocol discusses risks of five kinds for subjects participating in the repellency phases of the study: risks from exposure to the test material; risks from exposure to biting arthropods; risks from exposure to disease vectors; risks of physical stress in the test environment; and risks of stress from learning the results of a pregnancy test. Each class of risk and the steps taken to minimize it is discussed in pp. 5-10. The same classes of risk are characterized in the informed consent documents for treated and untreated repellency subjects on pp. 38-40 and pp. 48-50. There are two kinds of risks discussed for subjects in the dosimetry phase: risks from exposure to the test material; and risks of stress from learning the results of a pregnancy test; these types of risks are characterized in the consent documents for dosimetry subjects on p. 58.

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

No numerical probability is estimated. Potential subjects are told (with respect to the risks of contracting a disease carried by mosquitoes if they are bitten) that "there is a very sight possibility that you will contract a disease carried by mosquitoes if you are bitten, such as West Nile virus or equine encephalitis. This test will be conducted in an area in which such viruses have not been found in captured mosquitoes for at least two weeks. The risk is probably very low that any individual mosquito that might bite you carries a disease. In addition, since you are wearing repellent and/or other protective measures, and are carefully watching for mosquitoes that land and try to bite, you are probably at no more risk than you would experience when engaged in normal outdoor activities in a similar rural area at the same time of year." (page 36)

4.2 Risk minimization

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

Risks from exposure to the test material.

- Candidates with known allergic reactions to insect repellents and common cosmetics are excluded.

Risks from Exposure to Biting Arthropods and Risks from Exposure to Disease Vectors.

- The risk of a skin reaction to an insect bite is reduced by excluding candidate subjects who are aware of having a history of such reaction.

- Subjects will be trained to operate a mechanical aspirator to remove any biting insects that land on skin and how to identify insects that have landed with the intent to bite.

- In the field, treated subjects will expose small areas of treated skin for 4 minutes per hour. Untreated subjects will be protected with gloves, head nets, and Tyvek body suits. They will expose untreated skin for up to 2 minutes every half hour.

- The research is being conducted in an area where insect vectored viruses have not been detected by PCR-based screening of trapped mosquitoes from the test sites for at least two weeks, so the risk is probably low that any individual insect present carries a disease. Approximately 1000 mosquitoes of all species combined will be trapped for each sample and samples will be taken within two weeks prior to the test date.

- Of the diseases vectored by mosquitoes that may be present at the field site, only West Nile Virus (WNV) is of particular concern. The US Centers for Disease Control estimates that about 4 out of 5 people who are infected with WNV will not develop any type of illness. Subjects are instructed to be alert for any flu-like symptoms (unusual tiredness or unusually severe headaches, body aches, fever), glandular swelling or a rash on the trunk of the body, for up to two weeks after the test. About 1-in-150 infected people will develop more serious symptoms, which are described to the subjects. Most people (about 4 out of 5) who are infected with WNV will not develop any type of illness. Added risk from Western Equine Encephalitis and St. Louis Encephalitis, which present with similar pathology, is extremely low.

- First Aid materials will be available on-site.

- Epi-Pens will be on-site to treat anaphylactic allergic reactions.

- Subjects will be trained in the laboratory to handle mosquitoes using aspirators. Subjects will observe mosquitoes' behavior in the lab, and will learn how to remove them before they have time to bite.

Risks of Physical Stress in the Test Environment.

- A physician who has read the protocol and discussed the research with the Study Director will be on call on the day of field testing.

Risks of Stress from Learning the Results of a Pregnancy Test.

- Results of pregnancy testing will be observed by one female technician only and never recorded to minimize the stress on a female subject testing positive, and minimize the possibility that other staff or subjects may become aware of the results of that test.

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

The estimated dose rate is 14.3 mg/kg (Table 5 in page 20) based on predicted mean grams of lotion (rounded to 1 g.) applied by subject in prior Carroll-Loye Biological Research (CLBR) insect repellent efficacy studies (Table 4 in page 21).

The NOAEL for acute dermal LD_{50} of No Mas is greater than 5,000 mg/kg body weight. Thus, exposure of 14.3 mg/kg of lotion, containing 18.0% of combined active ingredients, results in an estimated MOE > 350.

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

"Stop Rules

All subjects

1. Consented duration reached.
2. Test site becomes unsafe for subjects for any reason.
3. Foraging pressure falls below threshold needed to challenge the test material.
4. Biting/foraging pressure falls below threshold needed to challenge the test material.
5. Sustained wind speeds exceeds 10 mph

Individual subjects

1. Subject asks to withdraw
2. Subject proves unattractive to target species
3. Subject's treated limb receives Confirming LIBe
4. More than one mosquito attempts to bite the treated subject's treated limb during any exposure period
5. Exhibits hypersensitivity to insect bites during test
6. Exhibits sensitivity to the test material during the test
7. Medical management is invoked for the subject (§1.3.6)" (pp. 25-26)

(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. 40)

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

"Subjects are clearly and repeatedly informed that they may remove themselves for any reason from the study at any time, without penalty to their compensation. All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash (a delayed hypersensitivity reaction) within 7 days of the conclusion of the test day.

"On the day of any study visit, staff will immediately communicate all subject concerns about health, safety, or comfort to the Study Director for assessment. The Study Director will also assess skin condition of affected subjects should any bites inadvertently occur during efficacy testing, or any subject reports any discomfort in treated areas. Subjects are instructed to inform the Study Director (i.e., the 'Principal Investigator'), or any other staff member if at any time during the study a subject suffers a skin reaction, such as redness, edema, itching or pain, or feels ill. Such subjects will be immediately withdrawn from testing and insect exposure, and medical management will be implemented. When a subject completes the study or is removed for any reason, treated skin areas will be gently washed with clean water and mild soap, rinsed with a 35% ethanol in water solution, then gently dried with a towel to remove test material.

"When medical management is implemented, the Study Director will contact the On-Call physician for the study and comply with the physician's instructions. On the day of testing, a physician who has read the protocol and discussed the research with the Study Director will be on call. Contact information for the nearest medical facilities and maps from the test site to the facilities will be prepared and on file before the day of testing. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will contact 9-1-1 by cellular or satellite telephone and cooperate as instructed with emergency personnel. Epi-Pens will be on-site. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject. We will be prepared to instruct emergency personnel on how to reach our site via multiple routes. In addition, we will personally transport affected persons to the nearest hospital if so advised by emergency personnel. There is sufficient redundancy in personnel that in such a case subjects remaining at the study site will still receive appropriate technical, scientific and safety guidance.

"Subjects may also request access to standard first aid materials (such as bandages, antiseptics, and mild topical and oral antihistamines) and request qualified first aid assistance at any time.

"As part of Medical Management, the Study Director will record all benign and adverse health observations." (pp. 8-9)

(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?

"Contact a physician and the Principal Investigator if you develop a rash within 7 days after the day of testing." (page 38) Irritant or allergic reactions to the test material or to mosquito bites are likely to occur shortly after exposure. Therefore, the seven-day period provides long enough duration to discover adverse events

(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 the insurance of a third party under which you are covered. 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 direct result of participation in the study." (page. 40)

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." (page 40)

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

"The principal beneficiary will likely be the Sponsor, for whom new data and new labeling will meet current U.S. EPA registration standards…For the general public, insect-borne disease is of growing significance in the United States and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities." (p. 10)

"[B]y serving as a participant, you may assist in making new insect repellent products available to consumers." (page 40)

(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. 10) Indirect beneficiaries would include those repellent users who prefer this product 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 formulation is effective in repelling mosquitoes, 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 formulation.

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 mosquito 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.

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

Complete records of the IRB review are provided in the protocol submission.

Satisfactory documentation of IIRB, Inc., policies and procedures and of IIRB, Inc., membership was submitted in addition to the protocol.

(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. 1)

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 pp. 16-17 of the protocol and the consent documents (pp. 33-62)

(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 the validity of the investigation be compromised.

9. Respect for Subjects

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

"Carroll-Loye Biological Research will retain records of this study indefinitely. You may access your own records by contacting the Study Director. Representatives from the sponsor (Sam Darling), the U.S. Environmental Protection Agency (EPA), the California Department of Pesticide Regulation and the Independent Investigational Review Board, Inc. (an independent committee that reviewed this study's ethical aspects to help protect the rights and welfare of study participants) may have access to all non-personal information collected in this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Any information or reports published as a result of this study will not identify you by name, or by any other personal identification." (page. 41)

"Results of a subject's [pregnancy] test are only observed by one female CLBR staff technician and never recorded to minimize stress on a female subject testing positive, and minimize the possibility that other staff or subjects may become aware of the results of that test." (page. 8)

Subjects are identified by name and subject number on the "Confidential Test Subject Information" form. On all other data collection forms, only the subject number is used. Recruitment of alternate subjects provides an opportunity for discrete withdrawal without explanation.

(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 (p. 14) 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 (page. 41).

Attachment 2

§ 26.1111 Criteria for IRB approval of research
Protocol No Mas 003 (7/15/10)

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 No Mas 003 (7/15/10)

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 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	pp. 33, 44, 55
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	pp. 38-39, 48-50, 58
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	pp. 40, 51, 59
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	Y	pp. 40, 51, 59
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	pp. 41, 51-52, 60
	(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 pp. 41, 51, 59-60 Medical Treatment pp. 40, 50, 59
	(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	pp. 41, 51, 59
	(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	pp. 33, 44, 55
(b) When appropriate, one or more of the following elements of information shall also be provided to each subject	(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	pp. 40, 50, 58
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	pp. 42, 52, 60
	(3) Any additional costs to the subject that may result from participation in the research	Y	pp. 41, 51, 59
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Y	pp. 41-42, 52, 60
	(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	N/A	
	(6) The approximate number of subjects involved in the study	Y	p. 35, 46, 56-57
(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	pp. 33, 44, 55

§26.1117 Documentation of informed consent
Protocol NO-MAS 003 (7/15/10)

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 forms pp. 33-62
(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 §3.4 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	

Attachment 5

40 CFR 26.1125 Submission of proposed human research for EPA review
Protocol No Mas 003 (7/15/10)

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. 5-10
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 5-10
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 10
		(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	p. 10
	§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. 198-224 (submitted) pp. 33-62 (approved)
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	pp. 12-14. 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. 16-17
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	pp. 194-340
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.		Y	pp. 335-336
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. 1-32 pp. 241-328 p. 33-62 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	 pp. 337-339 pp. 337-339 pp. 337-339 pp. 337-339 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. 194-340
	(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	Submitted separately
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		N	Submitted separately
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols

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