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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

September 9, 2019

MEMORANDUM

SUBJECT: Ethics Review of Completed Study titled, "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida"

FROM: Michelle Arling, Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs

TO: Linda Hollis, Chief, Biochemical Pesticides Branch
Biopesticides and Pollution Protection Division
Office of Pesticide Programs

REF: Dr. Emma N. I. Weeks (2019) Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida. February 6, 2019. 2732 pages. MRID 507791-01.

I have reviewed available information concerning the ethical conduct of the referenced research study, "Field Evaluation of Two Topically Applied Insect Repellent Products Containing IR3535 Against Mosquitoes in Florida". The documents submitted to the Environmental Protection Agency (EPA) describe the implementation and results of a field study, the objective of which was to determine the efficacy of skin-applied insect repellents against mosquitoes in field settings.

After reviewing all available documentation, I have determined that the conduct of this study met applicable ethical standards for the protection of human subjects of research, and that the requirements for documentation of ethical conduct of the research were satisfied. If the research is determined to be scientifically acceptable, I find no barrier in regulation to the EPA's reliance on this study in actions under the Federal Insecticide, Fungicide, or Rodenticide Act (FIFRA) or the Federal Food, Drug, and Cosmetic Act (FFDCA). If the research is not scientifically valid, it would not be ethical to rely on it.

In addition, under 40 CFR 26.1604, EPA is required to seek input from the Human Studies Review Board (HSRB) for intentional exposure human studies covered by EPA's Human

Studies rule that are initiated after April 7, 2006. EPA will share this study and all associated support documents, as well as EPA's science and ethics reviews of the study with the HSRB for their review. This memorandum and its attachments constitute EPA's ethics review.

Completeness of Submission

The materials provided by the University of Florida (UF) Repellent Testing Lab and the UFL IRB #1 satisfied the requirements of 40 CFR 26.1303. A checklist indicating how each requirement has been satisfied is provided in Attachment 1.

Summary Characteristics of the Research

LivFul, Inc. sponsored this study in order to determine the complete protection time (CPT) or duration of efficacy of skin-applied repellents containing 20% IR3535 (ethyl butylacetylaminopropionate). The study report describes testing two formulations of IR3535 products (lotion and wipe) applied to human skin against mosquitoes in the field. The study was initiated on May 18, 2018 and completed on February 6, 2019. Field testing occurred on August 15, August 19, August 26, September 1, September 8-9, and September 15-16.

Testing was conducted by the UF Repellent Testing Lab. The field tests of each product formulation were held at two ecologically-distinct sites in the Gainesville area ("a residential site in a suburban area … and a hardwood hammock site in a park", p. 22). A total of six test days were initiated, and four test days were completed. On two test days at one test site, mosquito landing pressure was too low, so the testing was stopped as required by the protocol. The test timeframe at the site was adjusted from daylight hours to dusk/evening hours and testing was completed.

Human subjects were used because no reliable models or surrogates have been found to adequately predict the duration of efficacy of topically-applied insect repellents. The repellent test product (IR3535) has been registered by EPA and has already been found to present little or no risk when used as directed. The precautions taken to mitigate hazards associated with the study were consistent with the approved protocol.

Required Reviews of Protocol & Ethics-Related Chronology

The draft protocol for this study was approved by the overseeing institutional review board (IRB), the University of Florida IRB #1 (UFL IRB #1). The UFL IRB #1 is registered with the Office of Human Research Protections (FWA#: 00005790). This IRB holds full accreditation from the Association for Accreditation of Human Research Protection Programs. Satisfactory documentation of the IRB procedures and membership were provided to EPA. Documentation regarding final IRB approval of the protocol and subsequent correspondence between the researchers and the IRB is included with the materials provided to the HSRB members.

An IRB-approved draft protocol was submitted to EPA for review. The protocol and EPA's review[1], dated June 29, 2017, were discussed at a public meeting by the HSRB on July 26, 2017. Per the final HSRB meeting report, dated October 26, 2017, the HSRB concluded that "[w]hen changes suggested by EPA and HSRB are incorporated, the proposed research will likely meet the applicable requirements of subparts K and L of 40 CFR Part 26."[2]

In follow-up to the HSRB meeting, the researchers revised the protocol and related materials to address comments, including the EPA and HSRB comments described in Attachment 2, and submitted the revised documents to the UFL IRB#1 for review and approval prior to initiating the study. The IRB approved the protocol on March 21, 2018, and approved the close-out of this study on December 20, 2018. p. 362.

Recruiting

Recruitment was conducted in substantial compliance with the protocol. The protocol called for 13 test subjects and two untreated control subjects at each test site on each test day, plus an additional five alternates. Multiplying this by the originally planned six test days, the goal was to recruit at least 120 subjects. The protocol was amended prior to subject enrollment to eliminate testing of one product formulation. *See* Amendment 2, p. 273. Therefore, the target number of subjects to be recruited was reduced to 80. A total of 70 persons were recruited for the study, 68 completed the consent process, and 38 subjects (20 males, 18 females) participated in at least one of the test days.

According to the protocol and completed study report, recruitment was conducted in the Gainesville area using "social media, newspapers, websites and traditional billboard advertising." p. 14. The IRB-approved advertising materials provided a brief explanation of the study and time required to participate, a few of the eligibility requirements, and the study director's contact information (email and phone). pp. 151-154. The advertisements also noted that subjects would be compensated for their participation.

The study director or a member of her research team contacted those who expressed an interest in participating by phone or email, using an IRB-approved script/email template. p. 155-157. This communication provided potential subjects with more information about the study, including the process for consenting, the screening process, eligibility criteria, and requirements for participation. Those who were qualified based on these criteria were invited for a meeting with the study team at the UF Repellent Testing lab to learn more about the study and to consent to participate.

---

[1] Fuentes, Bohnenblust, Arling. Science and Ethics Review of a Protocol for Field Evaluation of Three Topically-Applied Insect Repellent Products Containing IR3535. June 29, 2017. https://www.epa.gov/sites/production/files/2017-07/documents/ir3535_protocol_science_and_ethics_review_6-29-17.pdf

[2] Dawson, Liza. July 26, 2017 EPA Human Studies Review Board Meeting Report. October 26, 2017. https://www.epa.gov/sites/production/files/2017-10/documents/hsrb_july_26_2017_final_report.pdf

Consent and Enrollment

All participating subjects completed the informed consent process and signed the IRB-approved consent form. pp. 158-172. During the consent meeting, the study director or designee met with one or more volunteers, and discussed the consent form in detail. They gave a brief outline of the study, including its purpose, the subjects' potential role, the length of the study on a test day and overall, the pesticide to which subjects would be exposed, risks of participation and how they would be mitigated, and the eligibility criteria. The consent form and presentation highlighted that participation was completely voluntary. Subjects were permitted to ask questions in the group setting, and each subject was then asked by a member of the research team in a private setting whether they had any questions. All subjects signed and returned the consent form at this meeting; no subject requested to take the form home to consider it before enrolling in the study. Subjects were asked six questions to ensure their comprehension of the consent form. When the subject demonstrated comprehension, the individual was invited to consent to participate by signing the form. All subjects received a copy of their signed consent forms. After signing the consent form, subjects completed a screening questionnaire form. Then a member of the study staff confirmed eligibility through completion of the first three pages of the Case Report Form. pp. 175-266. If the person was determined to be eligible, the study staff verified the subject's age with a government-issued identification.

Subjects met the inclusion criteria outlined in the protocol. p. 16. Eligibility was confirmed through the subject questionnaire, mosquito attractiveness test, aspirator training, and pregnancy testing for female subjects. Subjects were eligible to participate if they were capable of following instructions and giving informed consent, between 18 and 55 years old, willing to undergo screening for attractiveness to mosquitoes and training on aspirator use, able to stand outside for at least 5 minutes at a time, and able to speak and understand English. People were not eligible to participate if doing so would pose a risk to their health (allergic or sensitive to mosquito bites, allergic to the test substance, skin disorders and/or open cuts/scrapes on the legs, previous anaphylaxis, compromised immune system). Additionally, pregnant or nursing women, and employees of the University of Florida and the study sponsor, as well as their spouses were not eligible.

After completing the consent process, subjects were scheduled for a training visit. This entailed the subject visiting the UF Repellent Testing Lab to be tested for attractiveness to mosquitoes and to be trained to use an aspirator. Mosquito attractiveness testing and aspirator training were conducted according to the protocol with one deviation. During the screening visit, a subject participated in the mosquito attractiveness test (exposure to mosquitoes but not to a test substance) prior to completing the screening questionnaire and pregnancy testing protocol. This subject did complete the pregnancy test and was not pregnant. This deviation was reported to the IRB, which "determined the deviation was not serious and not continuing and that no further action was needed." p. 323. However, as a result of this deviation, the Study Director prepared an additional checklist to ensure that screening, including pregnancy testing, would be completed prior to mosquito attractiveness testing or exposure to test substances.

Following successful completion of the screening visit, subjects were eligible to participate in one or more field tests.

Demographics

A total of 70 persons were recruited to participate in the study, 38 males and 32 females. Sixty-eight of those consented to participate in the study. Of the 68 persons who consented, 54 completed the screening phase (6 individuals did not qualify based on the questionnaire at the screening, 3 failed the mosquito attractiveness test, and 5 indicated after consenting but before screening that they did not have enough time to participate in the study), and 38 persons participated in at least one test day (20 males, 18 females).

Randomization and Test Day Procedures

For each test day, 20 subjects were invited to assemble at the University of Florida lab. Study staff checked them in as they arrived, verifying that they had followed the instructions to avoid scented products and vigorous exercise for 24 hours prior to the test day. The first 15 subjects to arrive and who followed the pre-test instructions were accepted as test subjects. The female subjects completed pregnancy testing to confirm their eligibility to participate. Once there were 15 fully qualified subjects, the alternates were dismissed. Subjects were randomly assigned for treatment or control by drawing slips of paper from a box. The lower leg for treatment was also assigned randomly. Lower legs of test and control subjects were prepared by the study staff, which involved rolling up the pant leg, marking the top of the test area with an eye liner pencil, washing the test area with unscented soap, rinsing with 70% isopropyl alcohol, and air drying the leg. After the test area was dry, it was measured following the steps outlined in the protocol. The dose was calculated by multiplying the surface area of the leg by the standard dose of 1 gram active ingredient/600 cm^2. Study staff measured the appropriate amount of repellent into a beaker and applied it to the subject's leg using a single gloved finger. Study staff applied the test substance to all test subjects and instructed them to protect the repellent treated legs from contacting anything.

Subjects remained in the lab for a period after the application, and then were transported from the lab setting to the field location in passenger vans arranged by the research team. The treated subjects and untreated control subjects were in separate vehicles. Upon arrival at the field test site, subjects were shown to screened tents with adequate seating and reminded of the guidelines for testing, including aspirating mosquitoes. Subjects received a bag containing their aspirator used during the aspirator training, as well as gloves and a head net to protect them from mosquito bites during the test or control exposure periods. Approximately two hours after application, the field testing began. To start, two untreated control subjects' lower legs were exposed to assess landing pressure, and needed to receive one landing in one minute for the testing to proceed. p. 83. Once landing pressure was established, the test subjects began 5-minute exposures to mosquitoes every 30 minutes. Repellency was measured as the time between application of a test substance and the first confirmed landing. A "landing" occurred when a mosquito landed on the treated test skin of a subject. A "First Confirmed Landing" is when two or more landings occurred in any five-minute exposure period or when one landing occurred in such an exposure period and another landing occurred in the next exposure period. After the initial landing pressure assessment, the two control subjects exposed one lower leg every 30 minutes to assess landing pressure, stopping at the sooner of five minutes or after five mosquitoes landed. All subjects remained at the test site until product failure or the maximum

test duration was reached, at which point they were transported back to the lab by the study staff. Researchers collected head nets, gloves, and aspirators, and subjects' participation was complete.

The test day procedures were conducted in substantial compliance with the ethical aspects of the protocol. When landing pressure was insufficient to continue testing (August 19 and August 26), the study was stopped. The EPA science review of this discusses the protocol and the EPA guideline requirements for adequate mosquito landing pressure on control subjects for the duration of the study, and the impact of landing pressure on EPA's interpretation of the study results.

Safety Precautions

The protocol discussed six potential hazards associated with these tests including exposure to mosquitoes and disease vectors, physical discomfort of mosquito bites, being outside in a hot, humid climate, adverse reaction to the test substances, unanticipated loss of confidential information, and psychological risks related to pregnancy testing. Risks were appropriately minimized as follows: Mosquitoes used in the attractiveness test and aspirator training were lab-raised and never received a blood meal. Testing was conducted in areas where no mosquito-borne pathogens were identified. The protocol requirements for trapping and testing mosquitoes prior to conducting field testing and coordination with the local health departments and mosquito control districts to ensure no vector-borne illnesses were detected at the test sites were followed. Subjects were trained in aspirating mosquitoes for the field portion of the test to avoid mosquitoes biting after landing and to collect the mosquitoes for pathogen testing.

Subjects who might have adverse reactions to mosquito bites or the test substance, or who might have difficulty standing outside for extended periods were excluded per the study's eligibility criteria. Subjects were provided with a head net and gloves, and instructed to wear clothing that fully covered their bodies during the testing. Only the area to be treated with the repellent was exposed to mosquitoes during the test period. In addition, untreated control subjects only exposed their lower leg until the requisite number of mosquito landings were observed for each period during the testing or until five minutes elapsed, whichever occurred first. At each test site, a shaded, screened area with chairs, with snacks, water, and other drinks was available for subjects' use during the periods between the test periods. Food provided took into account subjects' food allergies and sensitivities.

One adverse event was reported. During the course of the study (after enrollment closed but after testing had commenced), a subject reported to the Study Director contracting a skin rash that seemed to be poison ivy. The subject believed she had contracted it during the course of participating in the study, as the test sites were wooded locations. The subject treated her own poison ivy and did not seek medical attention. The Study Director reported this adverse event to the IRB. The IRB noted that while contracting poison ivy could be expected given the location of the test sites, the consent form did not explicitly disclose this risk. p. 48 The IRB recommended revising the informed consent materials, but this action was not taken because enrollment was closed and no further subject consenting was expected to occur.

Confidentiality

The study followed the measures outlined in the protocol regarding confidentiality. Subjects were identified by numbers on study documentation, rather than by name. Pregnancy tests were conducted in private and the results were only communicated with the Study Director or female member of the study team to confirm eligibility of female subjects to participate.

Compensation

Each subject received compensation consistent with the protocol and informed consent document. Compensation was $20 for participating in the consent meeting, $20 for participating in the attractiveness test and aspirator training, and hourly compensation for participation in each test day as described in the protocol. Once a test day began, no subjects withdrew or were removed from participation in this study.

Protocol Amendments and Reported Deviations

The protocol was amended a total of eight times, six times prior to initiation of testing (clarify protocol language for GLP compliance, test two products rather than three, clarify language in the protocol, add an additional recruitment method, clarify application techniques for test substance, and note that epi-pens would not be available during testing), once during testing (clarify several aspects of how testing would be conducted, including mosquito landing pressure on control subjects), and once after testing was completed (update the address of the study sponsor). p. 268-281. The amendment noting that epi-pens would not be available during testing also included a change in the screening questionnaire to exclude subjects who did not know how they reacted to mosquito bites to minimize the potential for enrolling a subject with an unknown severe allergy to mosquito bites. The protocol amendment and deviations related to mosquito landing pressure on untreated controls are discussed in more detail in the next section of this memo. None of these amendments directly impacted the health, safety, or welfare of the subjects.

One protocol deviation was related to the subjects' welfare. During the screening visit, a subject participated in the mosquito attractiveness test (exposure to mosquitoes but not to a test substance) prior to completing the screening questionnaire and pregnancy testing protocol. This subject did complete the pregnancy test during the same visit, and was not pregnant. This deviation was reported to the IRB, which "determined the deviation was not serious and not continuing and that no further action was needed." p. 323. However, as a result of this deviation, the Study Director prepared an additional checklist to ensure that screening, including pregnancy testing, would be completed prior to mosquito attractiveness testing or exposure to test substances.

Another deviation was related to a specific subject. The protocol called for contacting each subject within 72 hours of a test day to inquire about adverse effects. Despite attempting to contact this subject starting at 48 hours and making multiple attempts, the study team was unable to reach the subject until 73 hours after the test day. The subject noted that they were out of town and their phone battery was dead. The subject had no adverse effects and the deviation did not impact the subject's health or welfare.

Another subject-related deviation and subsequent amendment were related to the capture of all mosquitoes landing on test and control subjects during the test day. During testing, it became apparent to the Study Director that it was not feasible to capture all landing mosquitoes. Failure to capture all landing mosquitoes represented a deviation from the protocol for test days 1, 2 and 3. On August 27, the IRB approved a protocol amendment "to clarify that while attempts will be made to capture all mosquitoes that land on participants it is recognized that it may not be possible to capture every one as it is more important that the mosquitoes are not permitted to bite the participant and that the participants do not more from their positions". p. 279. This deviation and subsequent amendment were done to prioritize the subjects' safety and welfare by ensuring that the primary objective was preventing mosquitoes from biting subjects and collecting mosquitoes to the extent possible.

There were several protocol deviations reported to the IRB related to implementation of the testing that did not impact the health and welfare of subjects.

The EPA noted an issue related to amendment approval dates. The effective dates of some amendments predate the IRB's approval of the amendments. For example, for Amendment 2 the effective date is listed as June 16, 2018. p. 273. However, the IRB did not review and approve the amendment until June 17, 2018. p. 337. Amendment 7 lists the effective date as August 21 (p. 279), but the IRB did not review and approve the amendment until August 27, 2018 (p. 347). The discrepancies in the effective dates on the study did not affect subject safety or welfare; however, amendments are not effective until the IRB has reviewed and approved them. The EPA recommends that in future studies, the effective dates of amendments be listed as "IRB approval date" or left blank at the time of submission to the IRB and added after IRB approval.

Stopping Rules and Control Landing Pressure

The protocol had a stopping rule to avoid continuing a test day if there was not sufficient landing pressure on the untreated controls to demonstrate that the repellent was effective when mosquitoes were active. The IRB-approved protocol dated March 28, 2018 called for testing to stop "if more than 15% of exposure periods (based on the total number of projected exposure periods for the test) have low mosquito pressure measurements on the untreated controls". p. 85 It further stated that "if there is low landing pressure in more than 4 non-consecutive test periods over the course of the 14-hour test period, the test must be stopped. If the test period is shorter than projected, an assessment of whether the landing pressure was sufficient through the duration of the test will be made after the test has been completed." p. 85 The protocol was silent on whether subject testing should continue in the same exposure period where untreated controls did not receive an adequate number of landings.

The Study Director submitted to the IRB an amendment "[t]o clarify that a test period with low landing pressure is when both participants have less than 5 landings in 5 minutes. If one of the participants has less but one has 5 landings in 5 minutes or more this is considered adequate landing pressure for the purpose of stopping the study". p. 279. This amendment clarifies the landing pressure rate needed to allow the study to continue. The amendment also

specified in another point "that test periods that have low landing pressure will not be skipped only those with rain events will be skipped. A total of four test periods may be skipped or have low landing pressure. If a fifth test period is skipped or has low landing pressure than the study must stop." p. 279 The original protocol language about whether testing should continue if the control subjects did not receive sufficient landings was not sufficiently clear and led to questions while testing was occurring in the field. Recognizing the potential for different interpretations and after having a deviation from the protocol (see immediately below), the Study Director drafted this amendment, which was approved by the IRB on August 27, 2018. p. 347.

A protocol deviation occurred on test day 1, August 15, 2018. The Study Director skipped subject testing during periods when the control subjects experienced inadequate mosquito landing pressure. pp. 85-6. Three non-consecutive periods were skipped, which were not enough to require the Study Director to stop the study. Upon consultation with EPA, the Study Director indicated that she understood that testing was to continue with the subjects even during the exposure periods where control subjects did not receive an adequate number of landings, but that protocol requirements for stopping rules should be followed in terms of the total number of periods that could be skipped for weather or have inadequate landing pressure before stopping the study. As discussed above, the protocol was amended to reflect that testing should continue during periods of inadequate landing pressure consistent with the stopping rules, i.e., stop testing if a 5th period with inadequate landing pressure occurred. p. 279.

Apart from the deviation on test day 1, the Study Director conducted the study in compliance with these provisions. Testing was stopped on days 2 and 3 after the 5th period with inadequate landing pressure. Both test days 5 and 6 had four periods with inadequate landing pressure on both subjects, but no 5th period of low landing pressure occurred on either day. On each day, the testing was conducted in accordance with the protocol. EPA agrees with the Study Director's assessment that the deviation on test day 1 did not negatively impact the health and welfare of the subjects.

Applicable Ethical Standards

The following provisions of 40 CFR 26 Subpart Q define the applicable ethical standards which read in pertinent part:

> **§26.1703**: Except as provided in §26.1706, EPA shall not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1705**: Except as provided in §26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with all applicable provisions of subparts A through L of this part.

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

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

Findings

Pregnancy testing of female subjects was conducted on each day of testing. No pregnant or lactating women were enrolled in the study. All subjects who participated in study were at least 18 years old. Therefore, 40 CFR §26.1703 does not prohibit reliance on this research.

40 CFR §26.1705 requires that EPA have "adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part." Within this range, only subparts K and L are directly applicable to the conduct of third-party research such as this. After reviewing all available information, I conclude that this study was conducted in substantial compliance with subparts K and L.

As documented in Attachment 1 to this review, the central requirements of 40 CFR §26 subpart M, §26.1303 to document the ethical conduct of the research were addressed.

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

Conclusion

This study reports research conducted in substantial compliance with the requirements of 40 CFR 26 subparts A through L, and with the protocol for research that was reviewed by EPA and the HSRB according to the standards at 40 CFR 26, Subpart P. In its conduct, this study met applicable ethical standards for the protection of human subjects of research, and requirements for documentation of ethical conduct of the research were satisfied. From EPA's perspective, if this study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA's reliance on it in actions under FIFRA or §408 of FFDCA. This research and EPA's reviews will also undergo review by the HSRB.

Cc: Richard Keigwin
Robert McNally
Shannon Borges
Clara Fuentes
Eric Bohnenblust
Menyon Adams
Mary Rust

Attachment 1: §26.1303 Completeness Checklist
Attachment 2: Responsiveness to EPA and HSRB Ethics Comments on Draft Protocol

Attachment 1
§ 26.1303 Checklist for Completeness of Reports of Human Research Submitted for EPA Review

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

	Requirement	Y/N	Comments
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(1): Copies of • all research proposals reviewed, • scientific evaluations, if any, that accompany the proposals, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.	Y	Appendices 16.1, 16.2, 16.6
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of • members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution.	Y	Appendix 16.6
	§1115(a)(3): Records of continuing review activities.	N/A	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	Appendix 16.6
	§1115(a)(5): • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.	Y	
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	Y	Provided to EPA by the IRB
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).	N/A	
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a)(1): The potential risks to human subjects	Y	Appendix 16.1
	§1125(a)(2): The measures proposed to minimize risks to the human subjects;	Y	Appendix 16.1
	§1125(a)(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	Appendix 16.1
	§1125(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	Appendix 16.1
	§1125(a)(5): The balance of risks and benefits of the proposed research.	Y	Appendix 16.1
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Appendix 16.2
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	Appendix 16.2
	§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	Appendix 16.1
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	Appendix 16.6
	§1125(f): Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	Appendix 16.6
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research		Y	Appendix 16.2
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.		N/A	

Attachment 2

Responsiveness to EPA and HSRB Ethics Comments on Draft Protocol

EPA Recommendation	Action taken by Study Sponsor
Make editorial revisions and minor edits as recommended in EPA's written comments on Protocol V5 dated April 23, 2017. EPA provided the comments to the study sponsor and the HSRB in a file named Protocol_field_V5_05102017_OPP comments_06-29-2017.pdf	The study sponsor addressed these recommendations. See Appendix 16.1 for revised, IRB-approved protocol.
Add exclusion to exclusion criteria students of the primary investigator or any other University of Florida staff/faculty involved in the study	The study sponsor addressed this comment in the final IRB-approved protocol and consent materials. See Appendices 16.1 and 16.2.
Update the protocol to reflect the number of subjects and alternates necessary to ensure statistically-valid results.	The study sponsor revised the protocol to require 13 test subjects, 2 untreated controls, and 5 alternates per test day. See Appendix 16.1 for revised, IRB-approved protocol.
Revise Section 8.1.1. Site Monitoring to include coordination between the Study Director/staff and the local/state health department/mosquito abatement district. The Study Director should contact the local authorities weekly to inquire about any instances of vector-borne illness in the proposed testing areas. Additionally, monitoring should be conducted at the test sites for at least 4 weeks prior to the test day, and testing should not occur if any disease is identified in the test area within 4 weeks of the test day.	The study sponsor addressed these comments. See Appendix 16.1, Section 10.1.1.
Revise protocol to note that all adverse events and serious adverse events will be reported, and that all serious adverse events will be reported to the IRB for independent review, not only those deemed related and unexpected.	The study sponsor addressed this comment. See Appendix 16.1., Sections 8.2. and 8.2.2.

HSRB Recommendation	Action taken by Study Sponsor
Revise exclusion criterion from "any intervention study (other than an insect repellent study) in the previous 3 months" to "Participated in any other intervention study in the previous 3 months."	The study sponsor addressed this comment. See Appendix 16.1. The exclusion criteria were revised to read: • Participated in any other intervention study in the previous 3 months • Participated in a biting insect challenge test for the current study in the previous 72 hours
Revise section 17 and 19 of the informed consent form. The HSRB noted that "much of this template is inappropriate for an insect repellent study with healthy volunteers being conducted outside the confines of a hospital. Specifically, the researchers will not be creating protected health information and there is no reason to be sharing study information with the health professionals at the University of Florida or Shands hospital."[3] Make similar revisions limiting disclosure and protecting subjects' confidentiality to the protocol.	The study sponsor addressed these comments. See Appendix 16.2 (pp. 169-171) for the revised language in the informed consent form. See Appendix 16.1. for revisions to the protocol
Include on the consent form how many bites subjects are expected to receive (if any)	The study sponsor addressed this comment. See Appendix 2, starting on page 158.
Clarify the qualifications of the "first aider" who will be on site during test days.	The study sponsor revised the protocol to read "A member of the study staff who is a certified first aider (American Red Cross Adult First Aid/CPR/AED certified, or equivalent) will be present at all times to make these decisions during a test day." See Appendix 16.1, Section 8.1.

[3] Dawson, Liza. Human Studies Review Board Meeting Report. October 26, 2017. https://www.epa.gov/sites/production/files/2017-10/documents/hsrb_july_26_2017_final_report.pdf p. 11

HSRB Recommendation	Action taken by Study Sponsor
Revise protocol to note that all adverse events and serious adverse events will be reported, and that all serious adverse events will be reported to the IRB for independent review, not only those deemed related and unexpected.	The study sponsor addressed this comment. See Appendix 16.1., Sections 8.2. and 8.2.2.