EPA-HSRB-21-1

Dr. Jennifer Orme-Zavaleta

EPA Science Advisor

Office of the Science Advisor

1200 Pennsylvania Avenue, NW

Washington, DC 20460

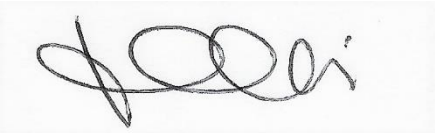
Subject: January 26, 2021 EPA Human Studies Review Board Meeting Report

Dear Dr. Orme-Zavaleta,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of a study protocol involving human participants. On January 26, 2021, the HSRB considered a study protocol for field evaluation of two topically-applied insect repellent products containing IR3535. Briefly, the goal of the proposed study is to determine the efficacy and duration of protection of two skin-applied products preventing mosquito landings on human hosts.

The HSRB's responses to the charge questions presented at the meeting on January 26, 2021 along with detailed rationale and recommendations for their conclusions are provided in the enclosed final meeting report.

Signed,



Jennifer Cavallari, ScD, CIH

Chair, EPA Human Studies Review Board

INTRODUCTION

On January 26, 2021, the United States Environmental Protection Agency (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to a study protocol "Field evaluation of two topically applied insect repellent products containing IR3535 against mosquitoes in Louisiana." In accordance with 40 CFR 26.1601, EPA sought HSRB review of the study protocol.

REVIEW PROCESS

The Board conducted a public meeting on January 26, 2021. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL- 10017-40-ORD). This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to the charge questions on ethical and scientific aspects of the completed and proposed research.

The Agency staff presented their review of the scientific and ethical aspects of the proposed research, with each presentation followed by clarifying questions from the Board. The HSRB solicited public comments and next proceeded to address the charge questions under consideration. The Board discussed the science and ethics charge questions and developed a consensus response to each question. For each of the charge questions, the Chair called for the Board to vote to confirm concurrence on a summary statement reflecting the Board's response.

For their evaluation and discussion, the Board considered materials presented at the meeting, study reports, related materials and documents provided by the study sponsors, the Agency's science and ethics reviews of the study, as well as oral comments from Agency staff and the investigators during the HSRB meeting discussions. A comprehensive list of background documents is available https://www.epa.gov/osa/january-26-2021-meeting-human-studies-review-board.

Protocol for Field Evaluation of Two Topically Applied Insect Repellent Products

Containing IR3535 against Mosquitoes in Louisiana

Charge to the Board- Science:

Is the protocol "Field evaluation of two topically applied insect repellent products containing IR3535 against mosquitoes in Louisiana" likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels mosquitoes?

HSRB Response:

The protocol "Field evaluation of two topically applied insect repellent products containing IR3535 against mosquitoes in Louisiana" is likely to generate scientifically reliable data, useful for estimating the amount of time each of the products tested repels mosquitoes provided that the comments and recommendations provided by the EPA and HSRB are adequately addressed.

Science review

The HRB reviewed the protocol and related documentation for the field evaluation of two skin-applied insect repellent products containing IR3535. The data collected in this study will be used to support product registration for AKIVA 20 lotion and wipe formulations of skin-applied repellent products containing IR3535. This study is designed to determine the median complete protection time (CPT). This study is sponsored by LivFul, Inc. and will be conducted by the London School of Hygiene and Tropical Medicine's ARCTEC and Louisiana State University (LSU).

Field-testing of these products has been conducted previously at two test sites. The HSRB reviewed the data generated to support this registration under a different protocol in October 2019. For this study, the proposed site will be selected from locations in Louisiana to replace data from a previous study at one Florida site where data were insufficient to support protection time for more than three hours due to low landing pressure from predominantly Culex species. Product registration requires data from two distinct sites. Data resulting from this study will be combined with existing data that support a CPT of 14 hours for the lotion and of 13 hours for the

wipe. The rationale for this testing is to collect data to show the efficacy of these products at repelling mosquitoes to support registration of these products by the EPA.

While the submission included two versions of a protocol (one dated 17 April 2020 and one dated 2 May 2020), both the EPA and the HSRB review pertain to the 17 April 2020 protocol version. EPA has provided a thorough scientific review of the protocol and supporting documents and made a number of recommendations that the HRSB agrees with.

Briefly, the field testing will be conducted in the following manner:

Control subjects will monitor ambient landing pressure by exposing their untreated leg for up to 5 minutes prior to each exposure period. Adequate landing pressure is defined as five landings within five minutes or less on both control subjects.

Immediately following the control subject landing pressure assessment, treated subjects will expose their treated limbs for five minutes every 30 minutes, beginning 2 hours post product application. Once the first confirmed landing has occurred within a five minute time interval (a single landing followed by a second landing within 30 minutes of the first recorded landing), the time point of repellent failure and period of complete protection will be recorded for that particular subject.

The test will be stopped for: safety reasons; more than four non-consecutive exposure periods or more than three consecutive exposure periods are missed due to bad weather, rain or wind speed >10mph; landing pressure is below acceptable levels for more than four non-consecutive exposure periods or more than three consecutive exposure periods; the end of field test period is reached (maximum duration reached or sufficient number of subjects experience FCL); at the Study Director's discretion for any reason.

We agree with the EPA recommendations as presented in their scientific review and report and would like to emphasize the importance of the following recommendations: revising the study objective and purpose with more detailed working; replacing references to bites with references to landings; adding details on randomization assignments; improving the site monitoring plan (including updates from the Local Health Department); assuring the presence of 3 species of mosquitos at the testing site; clarifying how the volume of the test substance will be applied;

clarifying skipped periods, CPT and landing pressure, delayed exposure periods; inclusion of additional data elements on field data forms; explicit criteria for subject withdrawal and replacement; clarification of statistical methods including Kaplan Meier Survival curves; and clarification with respect to the power analysis and statistical design.

Recommendations:

HSRB would like EPA to consider the following additional recommendations in a revised protocol.

Field site selection

We strongly support EPA's requirement that the test area be assessed for activity of all 3 mosquito species of interest prior to conducting the field testing. Failing to do so would seem to increase the likelihood of having less than sufficient data at the end of the study. HRSB concurs that a more detailed plan for site monitoring needs to be included in the protocol. In particular, we recommend that a 'trap type' be added to the description of the methods for site monitoring. The Study Director will be relying on information collected from the local health departments and mosquito control districts (MCD). In addition to specifying how the Study Director will coordinate with local these local agencies, please consider adding (as appendices) the SOPs for the MCDs of the testing locations/sites to further clarify the methods of site surveillance.

Dose application

In addition to the aforementioned need for detail on who will apply the test substance to subjects, HSRB further recommends that for consistency in application, it is best for one person to apply this dose. However, HRSB recognizes that this may cause interference with consistent times of application as a single individual may require time to work with each participant. HRSB recommendation is then for the researchers to ensure as best as possible, consistency in the application method for all participants.

Monitoring weather impacts

The protocol indicates that the study will be stopped for certain conditions of rain and wind. Study personnel should add to protocol that every effort will be made to check the weather conditions ahead of time and only schedule the field study in good weather.

Alternate study designs

While not part of the required review, the HSRB noted that the May version of the Protocol mentions a differing design of staggering time of 2 hours and 8 hours over two days. The HRSB wants to recognize some concerns if this were to be considered: 1) there needs to be consistency in how these studies are performed, 2) for the staggered individuals at 8 hours inside the building, the repellent on the skin is not subjected to as many weather events, which may or may not affect performance. In addition, EPA has mentioned that if for the 8 hours staggered individuals, mosquito landing occurred immediately upon entering field, then an earlier CPT could not be established. The HRSB agrees with this additional concern.

Statistical Review

With respect to the statistical aspects of the proposed study, the sample size for this study was appropriately computed using EPA guidance and calculations. There will be 13 individuals enrolled in the study with 2 untreated controls. Five alternates will be included for each product under study for a total of 20 participants per product or 40 total participants. The participants will be randomized to treatment or control within the males and within the females. Thus there will be one female control and one male control. Kaplan-Meier survival functions are appropriate to estimate the mCPT and 95% confidence intervals.

Recommendations

- HSRB recommends additional clarification of the randomization scheme. Specifically, detail to further clarify how the participants will be randomized to treatment or control is suggested. For example, with regard to sex, it is unclear how it will be ensured that one male and one female will be assigned as untreated controls
- The end of field test period is indicated as occurring when “maximum duration reached or sufficient number of subjects experience FCL”. The stopping rule for the ‘sufficient

number of subjects experience FCL' should be further clarified to indicate 'at least 50% of subjects experience FCL'.

- Clarification is needed with respect to how withdrawn participant data will be used in the statistical analysis. The protocol indicates that data from participants that have withdraw from the study will be used in the statistical analysis unless the participant requests that their data is not used. In its recommendations, "EPA recommends that a withdrawn subject whose data are right censored should not be replaced." The HSRB recommends to explicitly state that the data from participants that withdraw will be considered right censored in the statistical analyses. The definition of right-censoring should be clarified in the protocol.

Charge to the Board - Ethics:

Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Response:

The research proposed in the protocol "Field evaluation of two topically applied insect repellent products containing IR3535 against mosquitoes in Louisiana." and related documents is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L, if the recommendations made by the EPA and HSRB are adequately addressed.

Ethics review:

The EPA has reviewed the aforementioned protocol for a field testing at a single site of two formulations of skin-applied skin repellents containing IR3535 from both scientific and ethics perspectives. This study is designed to determine the median complete protection time (CPT) for AKIVA 20 lotion and wipe formulations of a skin-applied repellent containing IR3535. The repellents will be tested against mosquitoes in the field. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L.

The data collected in the study will be used to support product registration. The research has societal value because people are at risk of contracting mosquito-borne diseases, and the data

supporting currently registered skin-applied repellents do not show the efficacy of these formulations of products containing IR3535. The rationale for this testing is to collect data to show the efficacy of these products at repelling mosquitoes. As intended, the data resulting from this proposed study will be used to support registration of one or more of these skin-applied repellents.

The study team has implemented strategies and safeguards to minimize the risks of participants. Overall, the study activities are informed by prior research in this field that has been previously approved by the EPA and HSRB. The study products have been tested on human subjects in a similar study in Florida, the dose and exposure levels of IR3535 for this study are well below dermal toxicity levels and testing day safety procedures are thorough and well-documented.

The HRSB agrees that the testing periods should correspond with prior CPT findings for both the lotion (14 hours) and the wipe (13 hours) rather than the proposed 16 hours in the protocol. This will reduce unnecessary exposure to both the product and mosquitoes.

The HSRB agrees with the EPA recommendation that site landing pressure should be assessed and confirmed prior to field testing and that the project team should coordinate with local health officials to ascertain the presence of vector-borne illness at planned testing sites.

The HSRB agrees with increasing recruitment allowance to account for all potential participant discontinuation or withdrawal scenarios.

With respect to subject selection and recruitment, the strategy for equitable selection of subjects is adequate. The inclusion/exclusion criteria should be updated to reflect the suggestions put forth in the EPA review. Specifically, further rationale needs to be given for the age range of recruitment; specifically, if they agree with the EPA and will increase the age range beyond 55, or their justification for keeping it at the proposed 18-55.

Recommendations:

COVID-19 precautions

EPA has asked for COVID19 precautions to be included: wearing of masks and social distancing, and in general adherence to any CDC, local or state requirements. The HRSB discussed the following additional recommendations or considerations:

- Testing for SARS-CoV-2 prior to participation, testing of study team members who will be present on site can be considered. In addition, the HSRB recommends the incorporation of screening questions and/or temperature checks as relevant to identify study team members or participants at risk of infection or transmission.
- Data forms can include where the subject is to be located for each study period in the field, and where randomization is being used to place the participants at the site (i.e., seating layout of all subjects). This would facilitate contact tracing, if necessary.
- The protocol should also discuss what steps will be taken to address participants who fail to abide by social distancing and mask wearing provisions.
- The consent form and recruitment script should also note that subjects will be required to abide by mask wearing and social distancing requirements while participating in the study.
- The HSRB strongly supports EPA's comments concerning the issue of transportation to and from the test site, which is only vaguely discussed in the protocol and not in the consent form at all. Clarification is needed with respect to the options and/or expectations of subjects in terms of driving (e.g., can they drive their own vehicle to the test site if they prefer).
- We recommend adding follow-up contacts post-study to ask about possible symptoms or diagnoses. Furthermore, the collection of alternate contact information for someone who can reach the study participant if contact tracing is necessary.

<u>Prevention of heat stress</u>

Further clarification on what participants will wear (light clothes vs. Tyvek) during testing periods is required; otherwise, the study forms need to be harmonized and reflect the final proposed design. The HRSB recommends that no Tyvek suits be used; it is our understanding that Tyvek suits have not been utilized in other studies and present a heat stress risk. Due to heat related concerns, add a question and exclusion criteria for potential volunteers concerning

previous history of heat related injury (e.g. heat exhaustion, heat stroke, etc). Individuals that have experienced this in the past are more prone to future events. Excluding them from the volunteer pool could reduce overall risk to subjects. Furthermore, the HRSB recommends that fans be used in the enclosure for the comfort of the participants.

Consent form modifications

The consent form, as submitted, is inadequate and should include the following information as identified by the EPA:

- More information about the study sponsor
- More information about the pre-field-testing activities and requirements: attractiveness test; aspirator training and verification; COVID precautions; relative location of test sites and transportation thereto; and previously mentioned changes to compensation.
- The HSRB recommends that the risk section be constructed in a table form so that it's easier for participants to read, understand, and assess potential risks of involvement. If risks are supported by prior research or literature, then such phrases as "slight risk" should be further quantified (e.g., "less than 1% of people have X reaction") if possible.

The HSRB noted a number of inconsistencies across the protocol and supporting documents that should be reconciled.

- This include the factors that subjects are expected to refrain from the day before testing. The consent form and protocol, and recruitment events should all consistently mention all factors (i.e., spicy foods, not smoking etc.).
- Likewise, a net over the head and neck is mentioned in some areas is inconsistently presented across the materials. The protocol states that subjects will wear a head net and gloves during the study. The HSRB suggests clarifying whether these are disposable product and if new sets are provided to each subject.
- In several places the protocol refers to spray, lotion or wipe but it appears in others that only a lotion or wipe is to be used (there are also inconsistent references to 2 or 3 products). This should be corrected, as also noted by EPA.

- In the Protocol it is stated that the "Purity" of the test product is 20%. The expectation is that the concentration of the AI in the product is 20% but that the purity (i.e., concentration relative to contaminants, degradants) of the AI is actually much higher. This should be clarified.
- In various parts of the protocol it is stated that subjects who are allergic to any ingredients of the test material will be excluded (e.g., Protocol p. 7 emphasis added) but, aside from the AI, the ingredients of the test material are never discussed. So how is this potential allergy to be evaluated? If the check will be just against allergy to the AI, then that should be how the statement is given.
- It is stated on page 13 of the protocol that the results of the pregnancy test will not be recorded yet elsewhere it is stated that negative results will be recorded (protocol, p. 21). The protocol should be clarified for consistency.
- Regarding the recruitment script "If you have a known allergy to insect bites, or have participated in an insect repellent study in the last 3 months or insect repellent study in the past 72 hours you will not be able to participate in the study. " The wording is unclear and doesn't distinguish between the 3 month and 72 hour requirements. This is explained better elsewhere. "If you are an employee, manager, or spouse of employees of Louisiana State Univeristy and OR of the study sponsor, LivFul, you will not be able to participate in the study." Note also that University is mis-spelled. EPA's final comment on the "Survey Consent Form", final item "Signatures" is incomplete.
- It is unclear if the study team has a detailed procedure for guaranteeing that participants can use the aspirator with proficiency. For example, are a certain number of successful aspirations required before including someone in the study? It is unclear with the proficiency is tested or confirmed in the field.
- HSRB recommends clarifying whether participants and alternates be paid for shortened field-testing days (whether truncated by weather or inadequate landing pressure).
- While, the justification for the inclusion of English-speaking participants only (written materials are in English; study team speaks only English) appears acceptable. It is noted, though, that the fact that there are no direct benefits to participants is not generally considered justification for limiting study participation to people who speak a specific language.

- It is unclear whether participants who sustain “open cuts, scrapes, or skin problems” during the course of a field-test be withdrawn from the study. As this is an exclusion criterion, checking or querying for this before and during test days may be considered.
- The HSRB recommends clarifying the role of the Medical Monitor in assessing adverse events; it appears that the Study Director will have a large role in assessing and interpreting adverse events but does not have a medical/clinical background.