June 12th, 2017
EPA-HSRB-17-2

Robert J. Kavlock, Ph.D.
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1200 Pennsylvania Avenue, NW
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Subject: April 26, 2017 EPA Human Studies Review Board Meeting Report

Dear Dr. Kavlock,

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of mosquito repellency field testing.

The charge questions posed to the Board:

1. Does the HSRB agree with OPP's proposed approach from both a scientific perspective and an ethics perspective?
2. Does the HSRB have any comments on the proposed approach or ideas for additional limitations on such field tests? Please share those comments.

The Board's responses to the charge questions and detailed rationale and recommendations are provided in the enclosed final meeting report.

Signed,

Liza Dawson, PhD
Chair, EPA Human Studies Review Board

The HSRB appreciates the opportunity to comment on OPP's draft proposed guidelines[1] for field studies of mosquito repellency products.

OPP's proposal for additional guidance for repellency studies adds two additional criteria to the EPA guidance that already exists for these studies (OPPTS 810.3700: Insect Repellents to be Applied to Human Skin).[2] The proposal from OPP is the following (excerpt from OPP's background document provided to the HSRB):

> *If EPA continues to require field testing of mosquito repellents, OPP would like to place the following limitations on such field studies:*
>
> 1. *Field testing can only occur in locales where local transmission of Zika virus has not been detected by county or state health staff, mosquito abatement district staff and/or federal agencies. The study sponsor must confirm and document no earlier than 48 hours prior to each testing day that Zika has not been detected at or within the county encompassing the intended test site.*
>
> 2. *EPA is also considering asking study sponsors to apply the following exclusion criteria in addition to the criteria traditionally used; the following subjects would be excluded from these studies: (a) Males who plan on becoming fathers; and (b) Women who intend to become pregnant. Pregnant or nursing women are already prohibited from participating in intentional exposure human research studies. EPA's motivation for the additional criteria is the recognition that Zika virus infection during pregnancy can cause serious birth defects and is associated with other pregnancy problems; also, Zika virus can be transmitted through sex in addition to the bite of an infected* Aedes *species mosquito.*
>
>   *Consent forms should include information about Zika virus and its transmission. The training session which subjects attend should highlight the connection between Zika virus and the inclusion/exclusion criteria.*

HSRB response:

The HSRB recommends that OPP issue additional guidance about repellency testing, but does not recommend the specific language proposed above.

First, the Board would like to comment that most of the relevant issues are already addressed in existing OPPTS 810.3700 guidance. The specific recommendations relevant to risk mitigation are enumerated below under point (5).

[1] Background paper for HSRB on Mosquito Repellency Testing.10.27.2016

[2] EPA Product Performance Test Guidelines OPPTS 810.3700: Insect Repellents to be Applied to Human Skin

Furthermore, existing information from study designs used in field testing indicate that biting will not be used as an endpoint, further reducing risk of bites which results in low risk of transmission of pathogens.

The Board recommends that additional clarifying language can be added to supplement the OPPTS guidance as follows:

1. Given that is it possible to conduct field trials of repellent products in settings with extremely low risk of transmission of pathogens, there is an ethical imperative to select these low risk settings for studies. Rather than allowing study sites of uncertain background with regard to disease transmission and then needing to take additional risk mitigation steps such as choosing specific study populations or requiring contraceptive measures, the Board believes it is ethically more appropriate to choose very low risk sites, such that transmission through participation in a field trial is very highly unlikely to occur.

   The following is the rationale for this position:

   1) There is no ethical justification for allowing a <u>preventable</u> risk to occur when there is no corresponding benefit to subjects, site selection is the best mechanism to ensure low risk, and there is no scientific detriment to conducting studies using site selection as a primary method to reduce and manage risk;

   2) Even if subject selection were to be proposed as a further*, additional* risk reduction mechanism, in addition to site selection, it is likely to be an ineffective mechanism for reducing risk for the following reasons.

      (a) For some vector borne diseases such as West Nile Virus and Dengue, special populations such as pregnant women are not the only individuals who could be severely affected—making subject selection an ineffective way to reduce risk.
      (b) Even for pathogens like Zika which disproportionately affect clinical outcomes for pregnant women, fetuses and neonates, the risks of Zika being allowed to be transmitted to other, non-pregnant adults is a public health concern because of the potential for virus to remain in the body for many months and be transmitted sexually or through blood donation. The risk of creating a local transmission event is not limited to those individuals who are likely to bear children but would affect anyone who is likely to have sexual contacts with others, whether or not childbearing is associated with the sexual contact.

(c) Attempts to select individuals who are not likely to engage in sexual activity leading to pregnancy is difficult for behavioral reasons, because many people, both men and women, do not plan for pregnancy, or their plans or intentions may change. For therapeutic studies of products or interventions that are needed by a specific population to address their own health, it is reasonable to request that women (and men, in some cases) use contraceptive measures during a trial in order to reduce risks of unintended pregnancy and in order to assess the potential clinical benefits (or reap the clinical benefits) of a therapeutic product. But in the case of repellency testing, there is no such rationale. There is no benefit to the individuals in participating in a field trial, aside from the modest compensation offered and the altruistic satisfaction of contributing to science. This benefit to risk profile means there is no justification for allowing even a low level reproductive risk in these trials that would require contraceptive coverage—when it is possible to reduce the risk to negligible levels through other means.

3) For all of these reasons, it is not a reasonable option to conduct field studies in a setting in which Zika virus transmission, or for that matter other known pathogens such as Chikungunya (CHIK), Dengue (DENG), West Nile Virus (WNV) and others, are known to be locally transmitted or likely to be transmitted during a trial; therefore, the additional subject selection criteria would be a moot point;

4) Due to the reasoning above, the selection of field sites is extremely important and should be prioritized as the main risk management mechanism. The following are a number of considerations related to site selection. The HSRB recommends that study sponsors consult with OPP and with additional experts in vector biology and epidemiology of vector borne diseases as needed when determining site selection procedures:
    a. Sites should be chosen in locations with mosquito control districts that are actively engaged in surveillance and doing frequent monitoring for pathogens that can be detected in the mosquito population; since not all mosquito control districts are vigorous in this regard, sponsors should investigate the district's activity level prior to choosing sites. The Board notes that relying on centralized sources of information such as CDC may not capture all timely information, as local mosquito control districts do not always report to CDC frequently and there may be a significant time lag from emergence of pathogens and collation of the information on the CDC website.
    b. Sites that have had a recent history of local transmission of vector borne disease should not be chosen; the correct interval for determining

"recent" history should be longer than two weeks and the appropriate time frame should be chosen in consultation with experts in vector borne disease epidemiology to appropriate predict trends;

c. Sites should be selected in counties where the local health department is taking an active role in identifying cases of vector borne disease; in such settings an absence of cases due to local transmission is likely to be a better indicator of low risk, compared to settings in which surveillance is low or inconsistent;
d. Researchers should contact mosquito control districts and local health departments in planning stages of research to discuss the available data on whether there is local transmission of vector borne pathogens;

5) In addition to site selection, there are a number of very good guidance points in the OPPTS document that also reduce risk to human subjects in field trials. For ease of reference, those points are enumerated here.
    a. The Agency recommends landing with intent to bite as an endpoint. The choice of biting as an endpoint would need to be justified scientifically and the risks of pathogen transmission would need to be reassessed given the actual likelihood of bites. The use of landing as an endpoint significantly reduces risks to subjects (pages 7-8).
    b. Under Methods of risk minimization, page 12, the following are particularly relevant:
        i. Monitoring of field sites at least weekly for evidence of vector borne pathogens
        ii. Regular serologic testing of field specimens for evidence of pathogens
        iii. Training subjects to use the aspirator to collect mosquitoes before they bite, and conducting the training in a laboratory setting first prior to field trials so that only laboratory reared mosquitoes are used for training purposes;
        iv. Keeping in contact with subjects post-study to monitor any signs of study-related illness that could emerge
    c. Under "Specific guidelines for field studies of mosquito or biting fly repellency" the following points are also highly relevant:
        i. Again, recommends training in the laboratory for aspirating mosquitoes prior to biting (page 27)
        ii. Recommends choosing field sites with no evidence of prior transmission of vector borne pathogens in the prior two weeks. (page 27) This two-week interval could be increased to a longer interval such as 4 weeks or 12 weeks;

iii. Ensuring that the test area of skin (with repellent applied) is the only exposed area on the subject, and that all other areas of skin are adequately covered with bite-proof fabric (page 28);
iv. Having subjects exposed to mosquitos in intermittent periods to reduce fatigue (page 28);
v. Having subjects work in pairs to assist each other in identifying and aspirating mosquitoes (page 29);

d. The guidance also recommends that the study population be a representative sample of the user population, if possible, and that any exclusion criteria be scientifically justified (page 13)

The Board also recommends that the risk mitigation measures be described to potential study volunteers in the informed consent document and process, and that the rationale for conducting field trials with these measures be fully described. The informed consent process should inform participants that they can obtain more information about vector borne diseases, including Zika, Chikungunya, West Nile virus, and other diseases, from the CDC website, and further information should be provided to study participants who request it.

In summary, the HSRB recommends that study sponsors follow the OPPTS guidance from the Agency when designing studies, paying close attention to all risk mitigation measures in the guidance, as noted above, when designing field studies of repellency products. In addition, The Board recommends that study sponsors take special note of considerations for site selection. The combination of careful site selection, frequent monitoring of local health department and mosquito control district reports and data, and careful study design will ensure that studies are extremely low risk for human subjects.

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use.

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

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