Environmental Assessment for Investigational Use of *Aedes aegypti* OX513A

Source: Centre for Veterinary Medicine. **Environmental Assessment for Investigational Use of *Aedes aegypti* OX513A.** United States Food And Drug Administration. August 5, 2016. http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM514698.pdf (summary).

OX513A mosquitoes have been genetically engineered to encode a conditional or repressible lethality trait, which is a function of the overexpression of the tetracycline-repressible transactivator (tTAV) protein, and a red fluorescent marker protein (DsRed2). When tetracycline is not present (i.e., upon release of OX513A mosquitoes into the environment as in the proposed field trial), tTAV causes lethality in mosquitoes carrying at least one copy of the #OX513 recombinant DNA (rDNA) construct including the progeny of matings between OX513A males and wild-type females. The fluorescent marker can be used to identify the GE mosquitoes as larvae and pupae under laboratory conditions. More than 95% of OX513A progeny die before reaching viable adulthood if reared without tetracycline. Upon completion of the proposed trial, the population of *Ae. aegypti* is expected to be restored to its pre-field trial population level.

FDA's analysis in the Environmental Assessment is based on characterization of potential hazards and the likelihood of risk associated with investigational use of OX513A mosquitoes. Because risk is a function of hazard and exposure, if exposures are negligible, risk will also be negligible. These hazards and risks are described below, and FDA's findings drawn from that body of work form the basis of this finding of no significant impact (FONSI).

Toxic effects on humans or non-target animal health

Likelihood: extremely low. Risk: negligible.

- Almost all of the OX513A mosquitoes released as part of the proposed field trial will be male, and male mosquitoes do not bite humans or other animals.
- The trial protocol uses a sex sorting method based on the size difference between male and female pupae with quality control processes that ensure accuracy of sorting does not exceed a maximum of 0.2%.
- Thus, the overall probability of an OX513A female mosquito being released during the investigational trial is very low (0.2% at most) and the probability of this released female locating a human host and taking a blood meal is also low based on the estimated total human population in the trial area.

Allergenic effects on humans due to transfer of the rDNA construct to humans or non-target animals

Likelihood: extremely low. Risk: negligible.

- FDA determined that it is highly unlikely that the #OX513A rDNA construct could be transferred to humans or animals via biting because there is no known pathway for the naked, full length #OX513A rDNA to be present in mosquito saliva.
- If tTAV and DsRed2 proteins are expressed and secreted in saliva at all, these proteins are likely expressed below or close to the 1 ng range per Aedes female bite, which is much lower than the level at which known human allergens in mosquito saliva are expressed.

Increase in transmission of dengue or other diseases transmitted by mosquitoes

Likelihood: extremely low. Risk: negligible.

- OX513A male mosquitoes do not bite and, consequently, do not transmit diseases.
- A small number of females may be present at the site of the proposed release as a result of incomplete penetrance of the introduced lethality trait.
- Evidence suggests OX513A females have decreased vector competence because any OX513A females are expected to die in 2-3 days time, as the lack of tetracycline in the environment will turn on the lethality trait resulting in a lifespan too short to vector viral disease.

Increase in population of other mosquitoes that is opportunistic or via niche expansion that may contribute to the increase of disease

Likelihood: extremely low. Risk: negligible.

- the wild-type *Ae. aegypti* population would be expected to recover to pre-trial numbers after the cessation of OX513A mosquito releases.
- Therefore, the likelihood of adverse effects associated with an increase in the population of other mosquitoes that may contribute to the increase of diseases at the proposed trial site is extremely low.

Interbreeding with related mosquito species

Likelihood: extremely low. Risk: negligible.

- Mating in mosquitoes is very species specific.
- In the highly unlikely event that OX513A male mosquitoes do mate with other closely related mosquito species, it is highly unlikely that the rDNA construct would spread in the population of these mosquitoes due to the lethality phenotype conferred by this rDNA construct.

Adverse effects on predators, decomposers, or flora

Likelihood: Extremely low Risk: negligible.

- Because *Ae. Aegypti* breed in peri-domestic environments, they are subject to opportunistic predators that prey on their larvae and adults.
- FDA did not identify any specific parasitoid species associated with *Ae. aegypti*.
- In addition, no decomposers specific to *Ae. aegypti* were identified nor is a specific decomposer of detritus
- There are no reports indicating that *Ae. aegypti* mosquitoes are a pollinator for any plant species.

Development of resistance to insecticides

Likelihood: Extremely low Risk: negligible.

- Laboratory studies have shown that OX513A mosquitoes are susceptible to insecticides used for mosquito control.

Duration of Infant Protection Against Influenza Illness Conferred by Maternal Immunization: Secondary Analysis of a Randomized Clinical Trial

Source: Nunes MC, Cutland CL, Jones S, Hugo A, Madimabe R, Simões EA, Weinberg A, Madhi SA, Maternal Flu Trial Team. **Duration of Infant Protection Against Influenza Illness Conferred by Maternal Immunization: Secondary Analysis of a Randomized Clinical Trial**. JAMA Pediatr. 2016 Jul 5. doi: 10.1001/jamapediatrics.2016.0921. [Epub ahead of print].

Importance: Influenza immunization of women during pregnancy protects the young infants against influenza illness. The duration of this protection remains unclear.

Objective: To evaluate the duration of infant protection conferred by maternal immunization and its association with transplacental antibody transfer.

Design, Setting, and Participants: Infants born to women who participated in a randomized, double-blind, placebo-controlled clinical trial in 2011 and 2012 on the safety, immunogenicity, and efficacy of trivalent inactivated influenza vaccine (IIV3) during pregnancy were followed up during the first 6 months of life for polymerase chain reaction (PCR)-confirmed influenza illness. In a secondary analysis of a subset of infants, hemagglutination inhibition (HAI) antibodies were measured. The study was performed at a single center in South Africa. The secondary analysis was performed in October 2014.

Exposure: Maternal immunization for influenza.

Main Outcomes and Measures: The vaccine's efficacy against PCR-confirmed influenza illness and the percentage of infants with HAI titers of 1:40 or more by age group.

Results: There were 1026 infants (47.2% female) born to IIV3 recipients and 1023 infants (47.3% female) born to placebo recipients who were included in the analysis of the vaccine's efficacy. The vaccine's efficacy against PCR-confirmed influenza illness was highest among infants 8 weeks of age or younger at 85.6% (95% CI, 38.3%-98.4%) and decreased with increasing age to 25.5% (95% CI, -67.9% to 67.8%) among infants 8 to 16 weeks of age and to 30.3% (95% CI, -154.9% to 82.6%) among infants 16 to 24 weeks of age. Similarly, in the IIV3 group, the percentage of infants with HAI titers of 1:40 or more to the influenza vaccine strains decreased from more than 56% in the first week of life to less than 40% at 16 weeks of age and less than 10.0% at 24 weeks of age.

Conclusions and Relevance: Maternal immunization conferred protection against infection in the infants for a limited period during early life. The lack of protection beyond 8 weeks of age correlated with a decrease in maternally derived antibodies.

Trial Registration: clinicaltrials.gov Identifier: NCT01306669.