May 13, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Docket No. FDA–2014–N–2235

Re: Food and Drug Administration Docket No. FDA-2014-N-2235-0001; Draft Environmental Assessment and Preliminary Finding of No Significant Impact Concerning Investigational Use of Oxitec OX513A Mosquitoes

To Whom It May Concern:

The Biotechnology Innovation Organization (BIO) appreciates this opportunity to provide comments to the U.S. Food and Drug Administration (FDA) on the draft environmental assessment (EA)[1] and preliminary finding of no significant impact (FONSI) regarding the proposed field trial of the OX513A strain of *Aedes aegypti* (*Ae. aegypti*) developed by Oxitec.

BIO is the world's largest biotechnology trade association, representing small and large companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products.

Summary

Ae. aegypti, a non-native mosquito species that survives exceptionally well in urban environments, is the primary vector for yellow fever, a disease that is experiencing a resurgence in some tropical countries[2]. *Ae. aegypti* mosquitoes also carry and transmit other viruses – Zika, dengue, and chikungunya – that can lead to a number of devastating diseases, such as hemorrhagic fever, microcephaly in infants, Guillain-Barré syndrome, and other neurological disorders. Five field tests in three other countries have proven the release of OX513A mosquitoes is an effective method for decreasing the size of *Ae. aegypti* populations. These results are consistent with FDA's preliminary FONSI**.** The FONSI is well-reasoned and fully supported by the analysis in the draft EA. BIO

[1] https://www.regulations.gov/#!documentDetail;D=FDA-2014-N-2235-0001
[2] http://www.who.int/csr/don/archive/disease/yellow_fever/en/

urges FDA to move forward expeditiously, given the global threat to public health[3] posed by *Ae. aegypti.*

Health Threats Posed by *Aedes aegypti*

Ae. aegypti mosquitoes transmit a number of serious viral diseases, including the following:

- Yellow fever – Up to 50% mortality rate. Endemic in 44 countries in Africa and Latin America. The number of cases in those countries declined for past 10 years due to a global vaccine initiative begun in 2006. However, three African countries are experiencing an upsurge in reported cases (http://www.who.int/mediacentre/factsheets/fs100/en/).
- Dengue fever – Global incidence has grown rapidly with at least 2 million cases annually. Occurs in more than 100 countries around the world, with the Americas, South-East Asia and the Western Pacific being the most seriously affected. Cases were reported in Florida in 2013 and Hawaii in 2015. There is no cure and the first vaccine, registered in late 2015, is for very limited use in a few countries where the disease is endemic http://www.who.int/mediacentre/factsheets/fs117/en/).
- Chikungunya – has been identified in 60 countries in Asia, Africa, Europe and the Americas; no cure or vaccine (http://www.who.int/mediacentre/factsheets/fs327/en/)
- Zika virus disease – caused by an emerging virus with no available treatment or vaccine. The Zika virus is known to circulate in Africa, the Americas, Asia and the Pacific (http://www.who.int/mediacentre/factsheets/zika/en/). In the USA as of May 11, 2016, over 500 cases of travel-associated Zika infection had been reported in the 50 states, as well as almost 700 locally-acquired infections in U.S. territories[4]. Local viral transmission has been reported in many other countries and territories, and according to the World Health Organization (WHO), the Zika virus will likely continue to spread to new areas. On February 1, 2016, WHO declared Zika virus disease a Public Health Emergency of International Concern, and one week later the U.S. Centers for Disease Control and Prevention (CDC) elevated its response to Zika virus disease to its highest response level. Both health agencies have now confirmed Zika virus is a cause of microcephaly and other severe fetal brain defects[5].

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[3] In addition to yellow fever's resurgence, the World Health Organization (WHO) declared Zika is a global health emergency. The WHO estimates that as many as 4 million people could be infected with the Zika virus in the Americas in the next few years (http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika/en/).

[4] http://www.cdc.gov/zika/geo/index.html Accessed May 13, 2016

[5] http://www.cdc.gov/media/releases/2016/s0413-zika-microcephaly.html and http://www.cdc.gov/media/releases/2016/s0413-zika-microcephaly.html

Currently, prevention and control of dengue fever, Zika virus disease and chikungunya depend solely upon widespread implementation of effective mosquito control measures, because vaccines and effective anti-viral therapies for these diseases are not yet available.

Due to the severity of the viral diseases transmitted by *Ae. aegypti*, scarcity of options for prevention or cure, and insufficient government resources for effective vector control, public health and environmental agencies in a number of countries have approved field trials of OX513A[6] and have entered into agreements with Oxitec and other governments[7].

Field Trials of OX513A Mosquitoes

The OX513A mosquito is a strain of genetically engineered *Ae. aegypti* mosquito that contains a recombinant DNA (rDNA) construct that encodes a conditional lethality trait. Released OX513A males will mate with wild type *Ae. aegypti* females, but offspring of male OX513A mosquitoes do not survive to maturity, and therefore will not reproduce[8]. Based on earlier work, the expected result is a decrease in the overall population of *Ae. aegypti.* Field trials of OX513A conducted in a number of countries established the validity of the Oxitec approach: the size of the *Ae. aegypti* population in the targeted urban areas decreased from 82% to 99%. Finally, the offspring that inherit the rDNA construct die without reproducing, and as a result, no genetically engineered mosquitoes persist in the environment.

Thus, the OX513A mosquito will provide a highly targeted, ecologically sound means of mosquito control. In addition, it offers an alternative way to reduce *Ae. aegypti* populations that have evolved resistance to the insecticides used by U.S. municipalities in mosquito control programs. Data are now needed to assess the effectiveness of OX513A in decreasing *Ae. aegypti* populations in the U.S. This first proposed investigational use in a limited area in Florida will provide invaluable information that could ultimately help in decreasing illness and saving lives across the U.S.

Distribution of Aedes aegypti in the United States

Any person living in areas where *Ae. aegypti* occurs is at risk of being infected with the viruses transmitted by the mosquito (see Figures 1 and 2). It is a common mosquito in urban areas of southern Florida, and in cities along the Gulf coast of Texas and Louisiana.

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[6] Malaysia, Brazil (http://www.moscamed.org.br/2012/projeto-aedes/1), Cayman Islands, Panama (http://www.gorgas.gob.pa)

[7] http://www.oxitec.com/grand-cayman-use-oxitec-solution-suppress-wild-aedes-aegypti. Joint Statement of Continued Cooperation between the U.S. FDA and Brazil's National Health Surveillance Agency (ANVISA) regarding the Zika Virus Disease http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495211.htm

[8] Phuc, K.H., et.al. (2007) Late-acting dominant lethal genetic system and mosquito control. *BMC Biology* 5: 11

Figure 1. Geographic distribution of *Aedes aegypti* in the United States in 2005, showing both the usual range and the extreme range at that time[9].

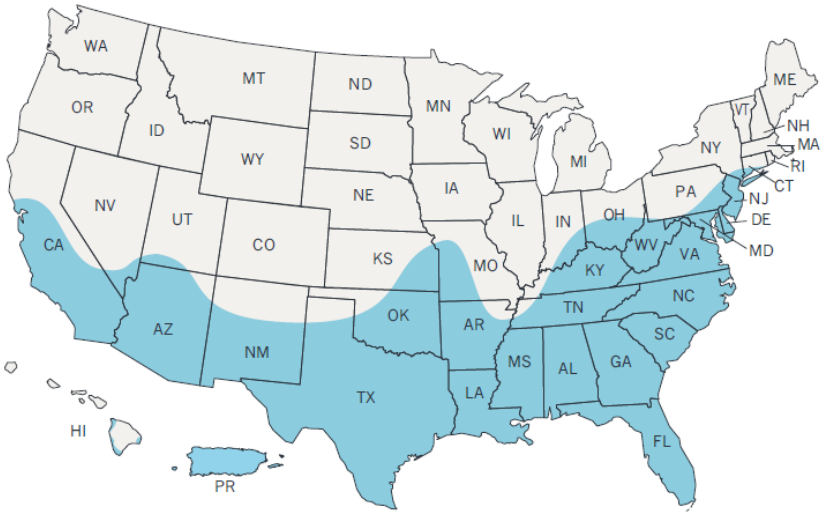

Figure 2. This map show CDC's best estimate of the potential range of *Aedes aegypti* in 2016 in the U.S. It includes areas where mosquitoes are or have been previously found[10].

[9] Darsie RF, Ward RA. 2005. Identification and Geographical Distribution of the Mosquitoes of North America, North of Mexico. University of Florida Press, Gainesville, FL.

[10] http://www.cdc.gov/zika/pdfs/zika-mosquito-maps.pdf

FDA Preliminary FONSI[11] and draft EA

The draft EA contains a comprehensive analysis of the underlying scientific issues, particularly as they relate to any potential hazard or exposure that might be associated with the proposed investigational use. As such, the draft EA far exceeds the applicable requirements under the regulations of the FDA and the Council on Environmental Quality[12].

FDA's expert review team carefully considered the potential environmental impact of the proposed investigational trial, as well as a no-action alternative. The team evaluated not only the data and information included in the sponsor's draft EA, but other data submitted by the sponsor, observations made by FDA inspectors accompanied by a subject matter expert from CDC during an inspection of a Florida Keys Mosquito Control District facility, and a visit to the proposed field study site.

The team concluded as follows. The consequences of escape, survival, and establishment of OX513A in the environment have been extensively studied, and that data and information from studies indicate that there are unlikely to be any adverse effects on non-target species (including humans). Risk of establishment or spread of OX513A mosquitoes was determined to be negligible. The duration of the proposed trial is short. Any unanticipated adverse effects are unlikely to be widespread or persistent in the environment. Significantly, the status of the environment is restored when releases are stopped; that is, the released mosquitoes all die, and the environment reverts to the pre-trial status. These considerations strongly support FDA's preliminary finding that the proposed field trial would not individually or cumulatively have a significant effect on the quality of the human environment in the United States.

Conclusion

The *Ae. aegypti* mosquito poses a major threat to the health of people living in areas where the mosquito occurs and vector control is difficult. In the United States, residents of 26 states and Puerto Rico are at risk of infection of four known viral diseases transmitted by this species of mosquito. As *Ae. aegypti* populations develop resistance to insecticides used in local mosquito control programs, public health offices must have access to other tools for decreasing the number of mosquitoes. The OX513A

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[11] FDA prepared the FONSI with the concurrence of experts from CDC and the U.S. Environmental Protection Agency, who participated in an interagency review team that considered possible impacts associated with the proposed field trial. http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM487379.pdf

[12] Indeed, actions on INADs are categorically excluded under the FDA regulations and, therefore, ordinarily do not require the preparation of an EA or an environmental impact statement. 21 C.F.R. 25.33(e).

mosquito could provide an ecologically sound measure of vector control. These field trials are an important means for confirming the effectiveness already demonstrated in trials outside the U.S.

USDA has used this paradigm, known as the sterile insect technique, for insect control quite successfully since the 1950's to eliminate insect pests of plant and animal agriculture. The difference is that USDA uses irradiation, rather than precise genetic modification techniques, to create male insects incapable of reproducing.

Given both the past success of the sterile insect technique in providing effective control with minimal ecological disruption and also the results of previous field trials of the OX513A strain of *Ae. aegypti* mosquito, BIO supports FDA's persuasively reasoned FONSI and urges the agency to move forward as quickly as possible with field trials, for investigational use, of OX513A. For all of the reasons previously discussed, FDA should also consider addressing the potential use of the Oxitec mosquito under the public health emergency provisions of the FDA's NEPA regulations.

Sincerely,

Brian Baenig
Executive Vice President, Food and Agriculture