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Public Interest Comment[1] on

The Food and Drug Administration's Public Availability of

Draft Environmental Assessment and Preliminary Finding of No Significant Impact Concerning Investigational Use of Oxitec OX513A Mosquitoes

Docket ID No. FDA-2014-N-2235

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The George Washington University Regulatory Studies Center improves regulatory policy through research, education, and outreach. As part of its mission, the Center conducts careful and independent analyses to assess regulatory actions from the perspective of the public interest. This comment on the Food and Drug Administration's draft environmental assessment and preliminary finding of no significant impact concerning investigational use of Oxitec OX513A mosquitoes does not represent the views of any particular affected party or special interest, but is designed to evaluate the effect of FDA's decision on overall consumer welfare.

Background

The Florida Keys Mosquito Control District (FKMCD) first consulted with Oxitec regarding its genetically modified (GM) OX513A mosquito for population control due to public health concerns about the spread of mosquito-borne diseases when 22 people in Florida's Key West were diagnosed with Dengue fever in 2009 and 66 in 2010. The FKMCD decided to test the effectiveness of OX513A by allowing Oxitec to conduct a field trial in Key Haven, Florida. The FKMCD is particularly concerned with the potential for *Aedes aegypti* to act as a vector for the transmis-

[1] This comment reflects the views of the author, and does not represent an official position of the GW Regulatory Studies Center or the George Washington University. The Center's policy on research integrity is available at https://regulatorystudies.columbian.gwu.edu/policy-research-integrity

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sion of diseases such as Dengue and Chikungunya, and most recently Zika virus. Although they have decades of expertise in combating mosquitos, several factors—including reductions in the effectiveness of insecticide use due to populations gaining resistance—result in an estimated maximum population reduction of 50% at best.[3] Field trials conducted in Brazil[4] and the Cayman Islands[5] estimate the effectiveness of OX513A around 90%, which would significantly decrease the risk of disease transmission[6] at potentially lower cost.

Oxitec's field trial has awaited FDA approval since 2011. As part of its approval process the FDA is required by the National Environmental Policy Act (NEPA) to assess Oxitec's submission of an environmental assessment (EA) and consider whether the evidence indicates that the trial could have a significant impact on the environment. FDA, in consultation with the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA) has published and made available to the public for comment a preliminary Finding of No Significant Impact (FONSI). Unless the public's input demonstrates any scientific evidence or area of consideration that FDA and its interagency group has not already considered, FDA will proceed to publish a final FONSI, allowing Oxitec to begin its field trial.

Evidence supports the interagency opinion that there is no appreciable risk to human or animal health or the environment. Further delays in allowing the field trial to be conducted or approving OX513A for commercial use in the U.S., pending the submission of data from a successful field trial, will continue to constrain the options available to limit the spread of mosquito-borne diseases and unnecessarily exposes the public to increased levels of risk—particularly in the event of an outbreak.

The unusually lengthy timeframe for FDA approval of this field trial in comparison to similar trials routinely approved by the USDA for the control of pests has already limited the number of effective tools available to combat the spread of dangerous diseases such as Zika, Dengue, and Chikungunya.

Statutory Authority

No laws specifically address the regulation of GM animals. Rather, U.S. agencies have successfully regulated GM products under their existing statutory framework since the Office of Science and Technology Policy (OSTP) issued the Coordinated Framework for Regulation of Biotech-

[3] http://www.oxitec.com/health/florida-keys-project/

[4] Carvalho et al. (2014). Mass Production of Genetically Modified *Aedes aegypti* for Field Releases in Brazil. *Journal of Visualised Experiments*

[5] Harris et al. (2012). Successful suppression of a field mosquito population by sustained release of engineered male mosquitos. *Nat Biotechnol* 30, 828-830.

[6] Focks D et al. 2000. Transmission thresholds for dengue in terms of *Aedes aegypti* pupae per person with discussion of their utility in source reduction efforts. *American Journal of Tropical Medicine and Hygiene*, 62(1):11–18.

nology (CF) in 1986.[7] Both USDA and FDA currently regulate genetically modified insects. USDA claims authority over GM insects considered "pests" under either the Plant Protection Act[8] or the Animal Health Protection Act.[9] To be considered a pest an insect must directly or indirectly injure, cause damage to, or cause disease in livestock or plants.

If it is not a pest, FDA claims jurisdiction over the GM insect. The Federal Food, Drug, and Cosmetic Act (FD&C) defines "articles (other than food) intended to affect the structure or any function of the body of man or other animals" as drugs. [10] Therefore, FDA currently regulates GM animals—including insects—under its interpretation that modified rDNA is a drug.[11] Since a "new animal drug" is "any drug intended for use for animals other than man," and since mosquitoes are not considered plant or livestock pests, FDA considers Oxitec's application for approval of its field trial of OX513A an Investigational New Animal Drug (INAD).[12] Pursuant to FDA regulations, sponsors opening a new INAD file must submit either a draft EA or claim categorical exclusion from the EA requirement.[13] Oxitec requires FDA approval before initiating a field trial because the FD&C Act makes it otherwise unlawful to introduce new animal drugs into commerce.

Oxitec's application to conduct its field trial in Key Haven, Florida has caused a significant amount of controversy, with many citizens arguing against releasing a GM insect to reduce mosquito populations. However, it should be noted that USDA scientists pioneered the use of releasing sterile insects for population control, known as the Sterile Insect Technique (SIT), more than 70 years ago and the agency has approved releases for more than 50 years with many documented successes. Among them is the eradication of the screwworm fly in North and Central America in 1966 which proceeded without any evidence of harm to the environment or humans. Incidentally, the first field test for using SIT was conducted in Florida on Sanibel Island.[14]

Compliance with the National Environmental Policy Act of 1969

FDA analyzed Oxitec's EA and drafted its preliminary FONSI as part of its requirements under the National Environmental Policy Act (NEPA)[15] which requires executive branch agencies to consider the environmental and related social and economic effects of proposed actions prior to

[7] https://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf
[8] 7 U.S. Code § 7701
[9] 7 U.S. Code § 8302
[10] 21 U.S. Code § 321
[11] 21 U.S. Code § 321 (g)(1)(C)
[12] 21 U.S. Code § 321 (v)
[13] http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm490246.htm
[14] http://www.ars.usda.gov/is/timeline/worm.htm
[15] National Environmental Policy Act Sec. 101 [42 USC § 4331]

making decisions.[16] FDA's regulations for implementing NEPA are located in Title 21 of the Code of Federal Regulations (CFR) Part 25.

> All applications or petitions requesting agency action require the submission of an EA[17]… the responsible agency officials will evaluate the information contained in the EA to determine whether it is accurate and objective, whether the proposed action may significantly affect the quality of the human environment, and whether an [Environmental Impact Statement] EIS[18] will be prepared… For a limited number of actions, the agency may make the FONSI and EA available for public review… for 30 days before the agency makes its final determination whether to prepare an EIS and before the action may begin.[19]

The Benefits of OX513A vs. Pesticides for Mosquito Control

Both EPA and USDA consider insect population control via the release of GM insects not only safe but the "environmentally preferable option"[20] due to its targeted nature compared to the use of pesticides. Chemical pesticides often have the unintended effect of also reducing populations of insects that are important food sources for birds and fish. They may also affect helpful insects that pollinate flowers such as bees. Additionally, pesticides are likely to have reduced efficacy over time as insects with higher resistance survive and pass on this resistance to their offspring. Federal regulations limit the number of pesticides available for mosquito control; the FKMCD has cited an appreciable decline in the effectiveness of their pesticides as one reason they look forward to expanding the tools in their arsenal for integrated pest management (IPM) to include OX513A.[21]

The Need to Target *Aedes aegypti*

Aedes aegypti is a particularly effective vector for the transmission of mosquito-borne diseases due to the fact that females primarily get blood meals from biting humans rather than other animals. As a result, they are a peri-domestic species which means they have adapted to live and breed close to human habitations. They are a known vector for transmitting Zika, Dengue, Chikungunya, West Nile, and Yellow Fever. Additionally, the potential elimination of *Aedes aegypti* is not an environmental concern due to the fact that they are not native to the Americas.

The OX513A Mosquito

[16] https://ceq.doe.gov/nepa/Citizens_Guide_Dec07.pdf
[17] 21 CFR 511.1(b)(10), 21 CFR 25.15
[18] 21 CFR 25.22
[19] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=25
[20] https://www.gpo.gov/fdsys/pkg/FR-2009-05-07/html/E9-10633.htm
[21] http://www.oxitec.com/health/florida-keys-project/

Oxitec's approach to insect control is a variation of the traditional SIT method, which uses radiation to make insects sterile and then release them to unsuccessfully mate with females, with the goal of greatly reducing or eliminating a target population of insects. Releasing sterile male mosquitoes by using radiation has not been effective since the dosage required to make them sterile reduces their fitness to a level where they cannot effectively compete with wild males to mate with females. Radiation is also expensive relative to genetic modification.[22]

OX513A was developed in 2002[23] and is the result of a genetic modification that causes the insect to release a protein (tTAV) that hinders its cells' ability to function, causing it to die. This autocidal trait is suppressed in the presence of the antibiotic tetracycline, which mosquitoes are fed in the lab. The required dosage is several orders of magnitude above what is found in nature. Therefore, OX513A and its offspring cannot survive outside of laboratory conditions. In addition to its lethality trait, OX513A is also modified to release a fluorescent marker protein (DsRed2) to aid in identification and data collection throughout field trials and other releases.[24]

Since female mosquitoes usually mate only once during their lifetime, the release of OX513A males reduces a population of *Aedes aegypti* because any females mating with OX513A produce offspring that are not viable. The release of OX513A males does not cause humans to face an increased level of exposure to mosquito bites because only females bite. The literature indicates that Oxitec has achieved a sorting accuracy to separate males from females in their facilities prior to release of 99.9%. Furthermore, samples of mosquitoes are collected before a release and manually counted by trained staff to ensure that the number of females present after mechanical sorting does not exceed 2%.[25]

Evidence Indicates Negligible Risk

FDA issued its preliminary FONSI after considering the evidence presented in the EA which includes data collected from successful field trials conducted in other countries. The following findings support the conclusion that the release of OX513A presents a negligible risk to the environment.

- Released mosquitoes die within two days as do their offspring, so they don't persist in the environment.

[22] Oliva, C.F., Maier, M.J., Gilles, J., Jacquet, M., Lemperiere, G., Quilici, S., Vreysen, M.J., Schooneman, F., Chadee, D.D., and Boyer, S. (2013). Effects of irradiation, presence of females, and sugar supply on the longevity of sterile males *Aedes albopictus* (Skuse) under semi-field conditions on Reunion Island. Acta tropica *125*, 287-293.

[23] Phuc et al. (2007) Late-acting dominant lethal genetic systems and mosquito control. BMC Biology, *5:*, 1-11

[24] Oxitec Ltd. Draft Environmental Assessment for Investigational Use of *Aedes aegypti* OX513A (2016)

[25] Harris et al. (2012), Carvalho et al. (2014)

- Mosquitoes would require roughly 746 – 2,500 times the concentration of tetracycline currently found in the environment of Key Haven, FL.
- Genetic modification has not resulted in OX513A responding differently to abiotic factors including response to temperature, resistance to pesticides, etc.
- Only males are released (with a 99.9% sorting accuracy,) and male mosquitoes don't bite.
- Unused females that are separated out prior to release are disposed of by incineration.
- Risks are negligible, even considering the small quantities of females that might be accidentally released, due to the fact that the proteins produced by the rDNA construct of OX513A (tTAV and DsRed2) were not detected in female mosquito saliva in lab tests. Additionally, neither tTAV nor DsRed2 are toxic or allergic to humans.
- "FDA concluded that the immunological response in humans and animals to OX513A female mosquito bites is not expected to be different from the immunological response to wild type *Ae. aegypti* mosquitoes."[26]
- *Aedes aegypti*, including OX513A, is not capable of producing viable offspring when mating with other species of mosquitoes.
- Gene transfer via blood feeding is not possible regardless of misinformed fears; there is no scientific evidence that supports the possibility of a causal pathway for this to occur.
- OX513A is fed blood meals in the lab using horse blood; this makes it unlikely that mosquitoes released into the wild will contain any diseases that affect humans.
- *Aedes aegypti* are not native to Florida and are not pollinators—their elimination is unlikely to result in unintended consequences to the environment.
- Finally, regarding a theory that gut bacteria within OX513A could become immune to tetracycline and disseminate this immunity within the environment: there is no causal pathway for this to occur since all gut bacteria are lost during the mosquito's metamorphosis from larvae to adults. Although larvae are treated with tetracycline, pupae and adults are not.

Recommendations

FDA should move forward to approve this field trial by issuing a final FONSI. There is no reason to believe that FDA should prepare an EIS given the lack of any evidence that this trial is likely to create a significant risk to humans or the environment. Furthermore, delays in conduc-

[26] FDA, Center for Veterinary Medicine. Preliminary Finding of No Significant Impact (FONSI) In Support of an Investigational Field Trial of OX513A *Aedes aegypti* Mosquitoes. March 2016.

ing U.S. field trials of the Oxitec OX513A Mosquito restrict access to a potentially powerful tool to combat the spread of very serious mosquito-borne diseases, such as Zika Virus. Data collected from field trials conducted in Brazil and the Cayman Islands suggests that OX513A is significantly more effective in reducing mosquito populations than traditional control methods, such as insecticides, with the added benefit of being a more targeted approach that could reduce the unintended effects of traditional control methods on other insects and the environment.

The only reasonable critiques of OX513A are based on the concern that we might lack data to validate Oxitec's claims about the effectiveness of their genetically modified mosquito. This argument states that the quality of data from field trials conducted in countries with less-developed regulatory regimes might not be reliable or poor data on existing pre-trial populations might not have allowed the establishment of a good baseline for ex-post measuring. Conducting a U.S.-based field trial presents an excellent opportunity to collect reliable field data.

Additionally, the FKMCD are experts in local mosquito control, have operated for decades, and maintain excellent data on mosquito populations. The FKMCD's involvement is also helpful in determining the effects of OX513A since they have a vested interest in ascertaining whether its use is safe, effective, and cost-effective. In any case, the field trial's approval is contingent upon an assessment of whether or not OX513A poses a significant risk to the environment, not on whether the product is actually effective. There is no scientifically verifiable evidence to support a claim that there exists any causal pathway for OX513A to have a significant impact on human or animal health or the environment.

Finally, the International Plant Protection Convention (IPPC)[27] considers targeted methods such as these as "among the most environment-friendly insect pest control methods ever developed,"[28] noting that they have been used successfully and without incident within the U.S. for over 50 years to reduce or eradicate insects considered pests that damage crops. If the use of GM insects is safe and justified to prevent damage to crops than we should certainly consider their use to improve public health outcomes—potentially saving lives by reducing human exposure to diseases such as Zika and Dengue.

[27] https://www.ippc.int/en/who-we-are/

[28] http://www.fao.org/docrep/009/a0450e/a0450e00.htm