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United States Senate

SUITE SD-255
DIRKSEN BUILDING
WASHINGTON, DC 20510-2107
202-224-2742

975 JFK FEDERAL BUILDING
15 NEW SUDBURY STREET
BOSTON, MA 02203
617-565-8519

222 MILLIKEN BOULEVARD, SUITE 312
FALL RIVER, MA 02721
508-677-0523

1550 MAIN STREET, 4TH FLOOR
SPRINGFIELD, MA 01101
413-785-4610

May 13, 2016

The Honorable Robert Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

The Honorable Gina McCarthy
Administrator
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Commissioner Califf and Administrator McCarthy:

I write to gain a better understanding of the use of genetically modified mosquitoes as a potential strategy to reduce the transmission of the Zika virus in the continental U.S. While reducing the population of the mosquito vectors using this technique could prove promising, many questions remain about the effectiveness and safety of the technology.

The Zika virus, first identified in humans in Africa in 1952, re-emerged in Brazil in 2015, and since then has spread rapidly through South and Central America and the Caribbean. According to the Centers for Disease Control and Prevention (CDC), 42 countries and territories have active local transmission of the virus, 38 of which are in Latin America and the Caribbean. As of May 5, 2016, the Pan-American Health Organization (PAHO) confirmed 8,672 cases of Zika in the western hemisphere, along with another 289,233 suspected cases.[1]

As of May 4, 2016 there are 472 cases of Zika in the U.S., which were acquired after travel to an area with active Zika transmission or through sexual transmission by a partner who has traveled to a high burden Zika country.[2] To date, individuals in 43 states and the District of Columbia have been diagnosed with Zika; 10 of these cases are in Massachusetts. Local transmission among U.S. territories is currently limited to Puerto Rico, American Samoa, and the U.S. Virgin Islands. Experts expect that Zika infected mosquitoes will appear along the Gulf Coast of the U.S. as the warmer summer approaches. Already at the forefront of this health emergency, residents in the four Border States with Mexico have been provided by the federal government with information on how to prepare for and protect against an influx of the virus.[3]

Transmission of Zika typically occurs from the bite of an infected mosquito. However, recent evidence also confirmed the disease can be transmitted through sexual contact. Although Zika is historically considered a benign virus resulting in mild flu like symptoms, recent investigations

[1] http://ais.paho.org/phip/viz/ed_zika_cases.asp
[2] http://www.cdc.gov/zika/geo/united-states.html
[3] https://www.epa.gov/border2020/zika-informational-resources-us-mx-border-residents

have discovered the alarming connection between the virus and the development of microcephaly, in which an infant is born with a much smaller head size and an underdeveloped brain, as well as Guillain-Barré syndrome, where the body's immune system attacks the nervous system, often resulting in paralysis. Additionally, other neurological abnormalities caused by Zika infection continue to emerge.

The main species of mosquito involved in the transmission of Zika virus is *Aedes aegypti*. The same mosquito is also responsible for spreading dengue, chikungunya and yellow fever. *Aedes aegypti* mosquitoes are endemic to all tropical and subtropical regions around the world. Another species, *Aedes albopictus,* is also thought to be a potential vector for Zika, and this species has a much larger population endemic throughout the U.S.[4]

One strategy being considered against Zika virus transmission is the release of genetically modified male *Aedes aegypti* mosquitoes that are engineered to produce offspring that die before reaching adulthood. The study focuses on the genetically modified male mosquito because unlike the females of the species, the males do not bite. A British company, Oxitec, originally developed this genetically modified mosquito to combat dengue fever. The company conducted several field tests, most recently in the Cayman Islands and Brazil. A second field test in the Cayman Islands is scheduled to begin in June, this time for Zika virus control. Studies of the genetically modified mosquito deployment in northeastern Brazil documented wild *Aedes aegypti* mosquito reduction approaching 95 percent.[5] Despite this significant reduction in the mosquito population, dengue fever and now Zika viral infections continue to spread in this area of Brazil.

Oxitec recently proposed to conduct a field test of the genetically modified mosquitoes in the Florida Keys in an effort to combat Zika transmission. As part of the Food and Drug Administration (FDA) review process, the company submitted a draft environmental assessment,[6] from which the FDA preliminarily concluded that there would be no significant impact on the environment.[7] The FDA is accepting public comments until today on the draft environmental assessment, and the residents of Key Haven, FL will be able to participate in a non-binding vote on August 30 to support or oppose the field trial.

This new use of genetically modified mosquitoes departs dramatically from the more traditional methods of controlling disease-spreading mosquitoes through use of insecticides approved by the Environmental Protection Agency (EPA) because a modified organism is being released into the environment. In light of this, and the dual role of the FDA and EPA in determining the safety, efficacy, and environmental implications of this technology, I respectfully ask that you respond to the following questions by June 13, 2016.

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[4] http://www.cdc.gov/zika/vector/index.html
[5] http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003864
[6] http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM487377.pdf
[7] Ibid.

1. Although the mosquito population was greatly reduced when the genetically modified mosquitoes were released in Brazil, dengue transmission and now Zika transmission is an on-going problem in that same geographic area. What is the explanation for this finding? Could the population of mosquitoes be reduced absent a reduction in the incidence of disease transmission in the Florida Keys? If so, please explain how the U.S. fight against the threat of Zika will be advanced through the use of these genetically modified mosquitoes.

2. PAHO has now confirmed that Zika virus is present in *Aedes albopictus* mosquitoes in Central America.[8] If the introduction of the genetically modified mosquitoes successfully suppresses the *Aedes aegypti* mosquitoes in Florida, is it possible for the Zika virus to extend or shift to the *Aedes albopictus* mosquito, a carrier that has a much broader range across the U.S.? Has either the FDA or EPA studied the implications of the virus transferring to a new host? Is it possible that dengue transmission was still occurring in the Brazil trial despite the elimination of the targeted mosquito because a different vector was the disease carrier?

3. A study in 2011 revealed that genetically modified mosquitoes matured slower, were smaller in size, and did not live as long as the mosquitoes that were not genetically modified.[9] While the draft environmental assessment indicated the success of reproduction would not be compromised by genetic modification, please explain field trial observations that could indicate modified mosquitoes would be at a disadvantage compared to the wild mosquitoes.

4. Other agencies including the EPA provided consultation on the draft environmental assessment, but the FDA took the lead because the genetically modified mosquitoes are classified as an animal drug. Given the potential environmental and ecological impacts of deploying these mosquitoes, including the intersection with other vector control strategies including insecticides, which are under EPA's purview, please explain how EPA feedback was requested, received, and ultimately incorporated into the draft assessment.

5. The draft environmental assessment indicated there would be no significant environmental impact of releasing the genetically modified mosquitoes during a proposed field test in the Florida Keys. The report indicated the potential for harm to human and animal health and the environment was low. However, there are a number of potential unintended consequences that should be explored at this stage. Please respond to the following:

    - The modified mosquitoes are engineered to require sufficient quantities of tetracycline in the surrounding environment (e.g., water or animal manure) for development to adulthood and are grown in the laboratory in the presence of tetracycline. Upon release from the laboratory conditions, the absence of tetracycline results in growth suppression and death. Antibiotics, including tetracycline, are known environmental contaminants.[10] Has the FDA or EPA planned for a scenario in which environmental conditions result in enough tetracycline to permit the growth of

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[8] http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=34243&lang=en
[9] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0020699
[10] http://link.springer.com/article/10.1007%2Fs10311-013-0404-8

the modified mosquitoes? What are the consequences of the modified mosquitoes not dying as expected?

- The draft environmental assessment stated it would be highly unlikely for the ribosomal DNA construct used to modify the mosquito genome to be inadvertently transferred to humans or other animals. However, this possibility cannot be ruled out, and may be facilitated by unknown symbionts or related species. Please explain how the agencies have prepared to address the impact should gene construct "spill over" occur in animals and humans.

6. It is possible that in preparation for Zika in the U.S., the public and local governments will increase the use of mosquito repellents, insecticides and larvacides as control measures against the threat of Zika. Under the Federal Insecticide, Fungicide, and Rodenticide Act, the EPA's insecticide registration process must include a dose-response assessment to examine the relationship between exposure and negative effects. Does the EPA plan to revisit the approval and use of registered insecticides due to the anticipated increased presence in water and on agricultural products? Please describe any such efforts that are underway.

7. The field trial in Florida requires a consistent release of genetically modified mosquitoes into a confined area in order to reduce the *Aedes aegypti* population. The draft environmental assessment indicates that, "immigration of mosquitoes into the trial site could compromise the effectiveness of the suppression objective."[11] Please describe how the trial in Florida can be made scalable to combat the spread of Zika throughout the greater United States, especially since the initial population size and immigration path of the wild *Aedes aegypti* mosquitoes cannot be anticipated or controlled.

Thank you for addressing these concerns. If you have any questions, please have a member of your staff contact Elyssa Malin or Jeanette Roberts at 202-224-2742.

Sincerely,

Edward J. Markey

Edward J. Markey
United States Senator

[11] http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM487377.pdf