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**Testimony before the U.S. House of Representatives**
**Science, Space and Technology Committee**

**"Science of Zika: The DNA of an Epidemic"**

**May 25, 2016**

Chairman Smith, Ranking Member Johnson, and members of the Committee thank you for inviting me to testify before your Committee today. My name is Hadyn Parry and since 2008, I have served as the CEO of Oxitec, a pioneer in using genetic engineering to control inspect pests that spread disease and damage crops. Oxitec was founded as a spinout from Oxford University and is a UK based subsidiary company of Intrexon Corporation, a New York Stock Exchange listed company which engineers biology to help solve some of the world's biggest problems.

**Background**

Oxitec Limited has pioneered the use of bioengineering to provide a solution for controlling the mosquito *Aedes aegypti* that spreads Zika virus. Oxitec developed its product OX513A, a self-limiting strain of *Aedes aegypti* in 2002 and since that date has conducted rigorous indoor and then outdoor evaluation and development. OX513A, therefore, has 14 years of data to support efficacy, environment and safety aspects. In all efficacy trials to date, Oxitec has demonstrated a reduction in the target *Aedes aegypti* population by over 90% in about six months. Over recent years, Oxitec has placed considerable focus and investment on its ability to scale up, supply and distribute its insects and OX513A should now be considered a fully operational solution, enabled to be deployed.

OX513A received a preliminary Finding of No Significant Impact (FONSI) from the Food and Drug Administration (FDA) in 2016 following an Investigational New Animal Drug (INAD) filing that was initiated in 2011. The public comment period ended on May 13, 2016 and a final opinion from the FDA is awaited before Oxitec has the regulatory approval to carry out a small trial in the Florida Keys as part of its application. We are hopeful that, in light of the public health need, FDA will act quickly to finalize its finding.

OX513A has national biosafety approval from the National Biosafety Technical Commission (CTNBio) for use in Brazil (April 2014) and Oxitec has been informed that we will shortly receive special registration from ANVISA, an agency within the Ministry of Health, to enable availability in Brazil.

OX513A has a specific recommendation from the World Health Organization (WHO) Vector Control Advisory Group for pilot deployment under operational conditions. WHO rarely recommends a specific product, but took this step as part of its emergency response and preparedness for the Zika virus.

**Oxitec's bioengineering technology and status**

**a) *Aedes aegypti***

While the current urgent threat is the Zika virus, the real target is the mosquito that carries the disease. Despite the present and widespread use of insecticides, over the last 50 years, there has been a sharp increase in both incidence and number of diseases spread by *Aedes aegypti* across the world. Before 1970, only nine countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. WHO reported an estimate of over 390 million dengue infections per year. Chikungunya came into the Caribbean in December 2013 and within one year, there were over one million cases across the Central America and Caribbean region.

By focusing on the mosquito, rather than the disease, Oxitec has accumulated years of development, well ahead of the Zika threat emerging. It also should be noted that it is unlikely that Zika will be the last disease transmitted by *Aedes aegypti.* It is clear that new tools are needed control this vector to guard against not only the current threat but also known threats such as dengue and Yellow Fever along with future, unidentified threats.

*Aedes aegypti* is the prime vector for Zika virus as well as for dengue, chikungunya and Yellow Fever. Understanding and then controlling the vector is key to controlling the spread of Zika or any other current or future virus transmitted by the mosquito. This mosquito species originated from Africa and has been spread around the world by human activities. This distribution has occurred via the transport of eggs, which are highly durable and easily carried in freight. Unlike many mosquito species which are adapted to the rural environment, this mosquito has adapted to be predominantly an urban one. It

bites humans by preference and lives in and around the home and other areas where people congregate. Its larvae and pupae develop in still water pools such as unused containers, birdbaths and blocked gutters. This mosquito can breed in as little as a bottle cap of water.

It is notoriously difficult to control with conventional insecticides not only because it has developed resistance to the most common insecticides but mainly because containers create multiple breeding sites in the urban setting that are often on private property and inaccessible to mosquito control staff. There are just too many dispersed inaccessible breeding sites that need to be continuously treated for this mosquito to be controlled through application of chemical insecticides.

Oxitec has used some key features of this mosquitoes' biology to design our solution. First, only females bite. Males cannot bite and, therefore, males represent no threat to humans.

Second, males are extremely effective at finding females. They tune in to the sound of the female wing beat to locate the female in order to mate. Once the female has mated successfully, she does not need to mate again and she will engage in a cycle of biting humans (to acquire blood), laying eggs, then biting again and will continue on this cycle. A single female can lay up to 500 eggs in her lifetime, which develop from egg to larvae to pupae to adult in a little over one month.

Third, it is important to note that neither male nor female mosquitoes have a significant spontaneous flight range. An adult mosquito will only fly up to about 200 yards in its lifetime.

**b) Oxitec's approach**

To control *Aedes aegypti*, Oxitec uses the mosquito against itself. We release males (that cannot bite) that mate with wild females. The offspring inherit self-limiting genes and die before becoming functional adults, thereby reducing the wild population. A male is biologically tuned to seek out females for mating purposes. The wild females cannot distinguish between an Oxitec OX513A male and a wild one, meaning that, provided sufficient Oxitec males are released across an urban area for a period of time, the population will rapidly decrease. In trials in several countries, we have shown that the population of *Aedes aegypti* may be reduced by over 90% in around six months. Moreover, as this species cannot fly far, the effect of the control can be highly specific to

the area of release. Specifically, we can treat broad urban areas by releasing in a pattern to cover a town or city, and we can modify the release rate to concentrate more on areas of higher mosquito population. Or we can even specifically target "hotspots". Once controlled, low level releases can be continued in areas of likely re-infestation to sustain the control over the longer term. Unlike chemical insecticides, the OX513A mosquito affects **only** the *Aedes aegypti* species, and has no measurable impact on other mosquito populations, or the overall insect population of the treated region.

**c) Oxitec's technology**

There are two key elements to the Oxitec bioengineering approach.

a) **A self-limiting gene.** Each released OX513A insect carries two alleles of the self-limiting gene meaning that each of its offspring inherits one copy. That single copy prevents the offspring from developing to become a functioning adult, so the offspring of a mating between an OX513A mosquito and a wild one die in early development. Oxitec uses the term self-limiting; meaning offspring will die before becoming functional adult. Therefore, these mosquitoes do not reproduce.

b) **A fluorescent biological marker.** In addition to inheriting the self-limiting gene, all of the offspring inherit a fluorescent marker. This gene allows us to identify all the larvae. When viewed under a filter, the larvae show a distinct red color and pattern. This color provides an unparalleled system for monitoring and tracing the Oxitec mosquito.

While the self-limiting gene is the mechanism to reduce the population of *Aedes aegypti* and, hence reduce the threat of transmission of Zika, the marker allows the program to be precise, efficient and cost-effective. Throughout a program, Oxitec collects eggs from the area of release and determines the proportion of the larvae that have an OX513A parent. More or fewer adult males then can be released in each area. The release rate is tailored to specific requirements and, as a result, overall control of the whole *Aedes aegypti* population is achieved as swiftly as possible.

**d) Programs, results to date and status**

An Oxitec program consists of the release of male mosquitoes from predetermined release points in a town or city each week. Global Positioning

System (GPS) release points are programmed into a release plan. Male OX513A mosquitoes are released from each GPS point from a moving van. The males then disperse and seek females. Eggs and larvae are collected each week from simple ovitraps (that are commonly used by most mosquito control teams) not only to show the level of *Aedes aegypti* population but also, using the marker, to adjust the release plan for the following weeks. The overall number of males used, the frequency of release and the number of release points are all determined at the commencement of the program and refined as it continues; the marker allowing for an unprecedented level of control and precision.

Oxitec has demonstrated over **90%** reduction in the *Aedes aegypti* population in about six months in all efficacy trials. Figure 1 shows the effect chronologically comparing an area of OX513A release (green line) against a site where no OX513A were released (a control area denoted by the orange line). Following first releases, the population starts to decline rapidly after about three months. As the population declines, releases continue but fewer OX513A males are used as they are not needed at the same level as when the wild population was higher. Even when the wet season starts, the wild *Aedes aegypti* do not recover in the release area with a continuing low level release. By contrast, the untreated area shows a reasonably consistent level of infestation throughout the year with a sharp seasonal rise in the wet season.

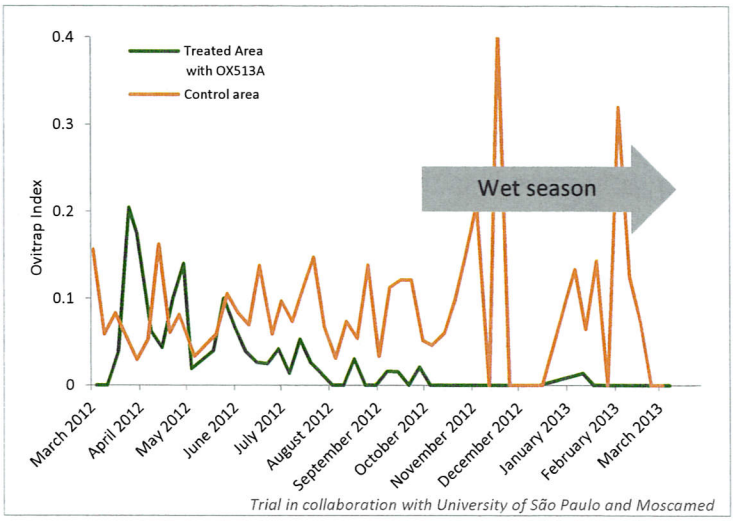


**Figure 1.** Oxitec's OX513A results in Mandacaru, Brazil suppressed *Aedes aegypti* by >90% and sustained control through rainy season

Oxitec has placed a major focus on operational preparedness. Oxitec has established permanent production units already in UK and Brazil and we are currently scaling up in Piracicaba, Brazil to a level to supply enough mosquitoes in the next phase to protect up to 1.5 million people. The supply chain can also use features of the mosquito biology to provide efficient logistics and quality control. Eggs can be produced at a central location for an entire country or region, from which they can be stored and distributed as required. More

locally, a production hub can receive eggs, rear to pupae, separate males from females and produce the males for release.

**e) Safety and environment**

Safety to environment and humans are key aspects of our approach. In stark contrast to insecticides (which will affect a broad array of insect life and respective food chains), Oxitec releases only affect the target mosquito so it is a species-specific approach. *Aedes aegypti* only mate and produce viable offspring with *Aedes aegypti.* Further, this species is an invasive or non-native one in all countries outside of Africa. From a historical perspective, it is a recent invader to the U.S. as well as an urban dweller so native ecosystems have not developed key dependencies. As a food source, it forms a very small part of the diet of other animals. For example, in the Florida Keys *Aedes aegypti* forms less than 1% of the biomass of all mosquitoes

But perhaps the most important environmental aspect of OX513A is that neither the released adults nor their offspring remain in the environment. Again, it is a self-limiting approach whereby the released males will die after a few days as will their offspring.

Over the last 14 years, Oxitec has conducted a broad array of studies on human safety and the environment and these studies have been used to inform regulatory decision making and these are publically available through the relevant country's regulatory mechanisms. Following the review of this data, the FDA's Center for Veterinary Medicine, working with experts from the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA), has reached a preliminary Finding of No Significant Impact (FONSI). This finding corroborates that of the National Biosafety Technical Commission (CTNBio) in Brazil where OX513A has been approved for releases throughout the country.

**Comparison to other forms of vector control**

The main forms of vector control used today throughout the world are a combination of monitoring, good practice (through the prevention or removal of breeding sites though regular inspections and eliminating sources of standing water) and use of insecticides. While insecticides have been the mainstay of vector control products, insecticide resistance and the urban anthropophilic nature of *Aedes aegypti* mean that insecticides are not effective in controlling population of *Aedes aegypti* across an urban environment.

In addition to insecticides, there are a number of new innovations proposed that range from Oxitec's OX513A with proven efficacy along with over a decade of data, to those still in the research phase or suggested for future research. Perhaps the clearest way to differentiate these new innovations is based on

a) whether the released insects are designed to spread and persist in the environment, or not; and
b) field trial evidence and operational preparedness.

**Spreading and persisting approaches (population replacement)**

One school of thought relies on the concept of replacing the population of *Aedes aegypti* with a different, modified version. This could be achieved through genetic engineering or through other means. Using genetic engineering, genes may be introduced through the mosquito population (gene drive) with the intent of replacing the existing population in a biased or driven way that is less harmful. There are different early stage gene drive research programs investigating this approach.

Another approach is to try to achieve the same outcome (population replacement) by infecting the mosquito population with a bacterium. Wolbachia is an intracellular bacterium that is not naturally present in *Aedes aegypti* but, once infected with a specific wolbachia strain (wMel), investigators report a reduction in the viral load in the mosquito in laboratory experiments. To date, outdoor trials have concentrated on replacement of the wild *Aedes aegypti* population with the wolbachia (wMel) infected strain. Efficacy trials to examine the disease impact have not yet taken place.

Regardless of how these prototypes are developed, one needs to both replace the existing mosquito population with the modified version but also ensure that the new modified version is significantly less of a threat over the long term than the wild *Aedes aegypti* that it replaces. Both males and females will need to be released in order to allow the modified mosquito to replace the wild version. If the mechanism of action results in a reduction in virus rather than a complete block, then releasing biting females when virus is endemic may actually assist virus spread.

In practice, population replacement is more complex and a potentially riskier strategy than that of use of Oxitec's technology, since population replacement results in a new population of mosquitoes modified either by genetic means or

through infection with a bacterium. It is therefore essential to consider the long-term impact of the evolving mosquito combined with the bacteria and combined with virus. A particular focus for products that are designed to spread and persist in the environment is the potential long-term effects as by their nature there is no obvious ability to contain the spread or engage a product recall if this is required. Stewardship will also be a key issue.

**Non-spreading and non-persisting (population reduction)**

Population reduction approaches rest on using products that do not persist or spread in the environment. The product is used for as long as it is required and no longer. Some may argue that long-term control means ongoing releases but in effect we already have ongoing (but inadequate) vector control with chemical products. The ability to suppress populations of disease-carrying mosquitoes without ongoing consequences is a key advantage of these approaches.

Oxitec is a leading proponent of this approach with OX513A. Both the released males and their offspring die, meaning that there is no spreading in the environment and no persistency.

There is also significant precedent in this approach in agriculture through the Sterile Insect Technique (SIT) that was developed using radiation in the 1950's and 1960's. The use of radiation devices can impose limitation on deployment and the damaging nature of the radiation can weaken the mating fitness of the insects. Mosquitoes have been a key target for radiation driven SIT but have enjoyed mixed success over many years. *Aedes aegypti* radiation based programmes have been suggested as a response to Zika but no field trials have yet taken place so the applicability of radiation-based SIT to *Aedes aegypti* is not yet tested or proven.

**Field trial evidence and operational preparedness**

A key consideration is that Oxitec commenced its development in 2002. At that time Oxitec's core focus was *Aedes aegypti* due to the unmet need to control this vector with respect to dengue. Even since 2002 the geographic spread of dengue and the number of cases has risen alarmingly. To this has been added the Chikungunya epidemic and now Zika. But this singular focus on the vector has meant that Oxitec's OX513A has accumulated an extensive body of efficacy and other supporting data, especially since first outdoor trials in 2009. Ironically as a genetically engineered organism it has undergone arguably a far

higher standard of regulatory and independent scrutiny than non GE approaches.

Also, development has focused on operational practice, namely the development of methodologies, quality control and standards that have arisen as part of the maturation of the program. This level of data and operational use preparation sets OX513A apart from other approaches that are much earlier in research and development cycle.

**Regulatory Status with a focus on the United States**

The regulatory environment for all new approaches should be predictable, consistent and rigorous. The innovation that is needed in the area of vector control is stifled when regulatory delays occur. When serious diseases are involved, these delays can have life-altering consequences.

Oxitec's involvement in the United States began in 2009-10 when the Florida Keys experienced local transmission of dengue. The Florida Keys Mosquito Control District (FKMCD) determined that they needed new tools in order to protect their citizens from the mosquito that is the main disease vector: *Aedes aegypti*.

FKMCD sought the opportunity to evaluate Oxitec's technology, and it was agreed to conduct a small scale efficacy trial in a defined area in the Florida Keys to test our technology for the control of *Aedes aegypti*. Oxitec initially applied to USDA-Veterinary Services for permission to conduct the trial. In 2011, USDA-VS determined that it did not have regulatory authority over the Oxitec mosquitoes as it could envisage no risks to animal health from its use. Therefore, in the absence of another regulator, the FDA-CVM assumed regulatory responsibility by regulating OX513A under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). As set forth in FDA Guidance on Genetically Engineered Animals (referred to as "Guidance 187"), the agency regulates genetically engineered animals under its new animal drug authorities on the basis that the recombinant DNA construct introduced into the genome of the animal is intended to affect the "structure or function" of the animal and, thereby, meets the "drug" definition under the Act. As a result, genetically engineered animals are subject to mandatory pre-market approval by FDA.

In late 2011, Oxitec opened an investigational new animal drug (INAD) file with the FDA-CVM for a small scale efficacy trial in the Florida Keys, building on the promising efficacy results from Brazil and Cayman. While the recombinant

DNA introduced into Oxitec mosquitoes is regulated by FDA as a new animal drug, bacteria, such as wolbachia, that are introduced into mosquitoes as a form of vector control are regulated by the Environmental Protection Agency (EPA) as pesticides. The impact of this distinction in regulatory jurisdiction is substantial as there are significant procedural differences between FDA's and EPA's approval pathways. The FDA regulatory process for new animal drug approval is rigorous and multi-faceted. Companies seeking FDA approval generally must provide considerable and comprehensive data and information to establish safety and effectiveness, perform an in-depth assessment of environmental impacts, develop drug labeling for FDA approval, and otherwise comply with several pre- and post-market regulatory requirements. In order to assess environmental impacts, FDA-CVM brought together regulators from EPA and CDC as well as other experts for this evaluation - this took a considerable time to form the review team (6-9 months) as the agencies negotiated a memorandum of understanding to govern the interagency consultation. Meanwhile, Oxitec, as the regulated company, was prevented from moving forward with the efficacy trial in the Florida Keys.

FDA-CVM operates a modular dossier submission structure and Oxitec provided the first module in Dec 2013 and the last in Feb 2016, which was the final version of the sponsor-authored draft environmental assessment (EA) prepared in accordance with NEPA requirements and originally submitted to FDA in 2014. No items are outstanding from the FDA-CVM review for the efficacy trial and Oxitec has received letters of adequate response from FDA-CVM on modules submitted. Following this lengthy and time-consuming pre-trial process, FDA published on March 14th 2016 the draft Environmental Assessment (EA) for public comment along with a preliminary finding of no significant impact (FONSI) on human or environmental health. The public comment period was initially set for 30 days and the period was further extended for an additional 30 days at the request of non-governmental groups such as the Center for Food Safety. The public comment period finally closed on May 13th 2016, following the submission of over 2500 public comments. FDA-CVM is now required to review these comments for substantiveness and will prepare a final EA. Thereafter, Oxitec should be able to move forward with the efficacy trial in Florida. Given the urgency of moving forward, we hope that FDA will make the review of these comments one of its highest priorities and finalize their assessment quickly.

In the Keys, both the FKMCD and Oxitec have proceeded with a policy of transparency. The positive for this is that it allows for public information to accrue over a period of time. Interestingly, since 2013, there have been a

number of public surveys that -- despite the absence of recurring disease transmission in the Keys -- show a consistent level of strong support for the approach. A recent study by Purdue University reports 78% support respondents for the use of GE mosquitoes as part of the battle against Zika.

There will always be a divergence of opinion for any new intervention and there are those who are against the trial. The Florida Keys Mosquito Control Board has now agreed to hold a referendum in Monroe County to ascertain local opinion on the trial being carried out. This is likely to occur in August 2016.

In Brazil the first trial with the Oxitec mosquito, OX513A, was conducted in 2010 in Juazerio, Bahia, NE Brazil. This was followed by additional trials. These trials demonstrated no adverse effects resulting from the release of the Oxitec mosquitoes. Moreover, the trials generated sufficient data to submit a commercial application to the Brazilian National Biosafety Technical Commission (CTNBio) in July 2013. In April 2014, CTNBio approved Oxitec's application for use of the Oxitec mosquitoes throughout Brazil.

Oxitec has been informed that we will shortly receive special registration from ANVISA, the Health Agency within the Ministry of Health, to enable widespread availability in Brazil. Oxitec should therefore be able to bring OX513A into use throughout the country to support the fight against Zika.

**Figure 2.** Brazil press describe Oxitec solution as 'The Friendly Mosquito'

In Brazil, both dengue and Chikungunya are endemic and Zika has come into the public consciousness with alarm from 2015. Public support for the Oxitec approach has been at a high level – up to 96% support in Piracicaba; the first operational project. The Brazilian press has been almost uniformly supportive and indeed have given OX513A their own name describing it as *Aedes aegypti do Bem* or 'the friendly mosquito'.

Whilst at the time of writing there is no known local transmission of Zika on the United States mainland, local transmission is expected by many experts. However, there is already significant transmission in Puerto Rico and the first microcephaly case.

Considering it has already taken over 3 years due to a lack of clarity of the regulatory process for the analysis of a small scale efficacy trial we urge FDA to do the following:

a) expedite the final review of this dossier;
b) consider using its enforcement discretion to allow for rapid review of future environmental assessments, given the low risk profile of this product; and
c) given the current Zika crisis, grant emergency use or other expeditious regulatory solutions for the widespread approval of this promising vector control tool.

In conclusion, this technology has a very real potential of assisting in preventing and mitigating the Zika public health crisis. Here in the US and globally, I hope that we can work with the Congress and the Administration to expedite the approval and adoption of this promising technology. Our hope is that communities will have meaningful access to this technology in a timely manner as part of an integrated vector control approach. Mr. Chairman, Ranking Member Johnson, and members of the Committee, thank you for the opportunity to testify today and I look forward to answering your questions and working closely with you in the weeks ahead.