OXITEC

PAHO Evaluation Group meeting on Aedes

5th December 2017

Oxitec Ltd.

5th December 2017 Simon Warner, CSO Oxitec

Topics

1. Overview of OX513A technology

2. Overview of regulatory assessments and decisions

1. Overview of OX513A technology

Who is Oxitec?



We provide insect control through novel technology that improves human health and food quality

Through the reduction of the insect population

Biological approach that is sustainable, economic and applicable to many insect species worldwide

Focus on Aedes-borne diseases

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Dengue

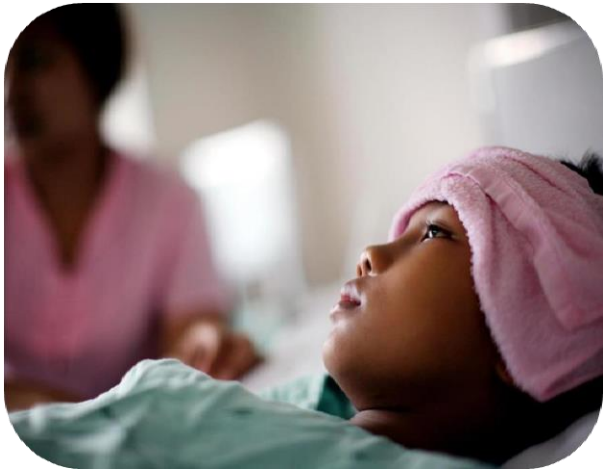
40% of global population at risk; 390 million cases/year[1]; costs US$380 billion/year

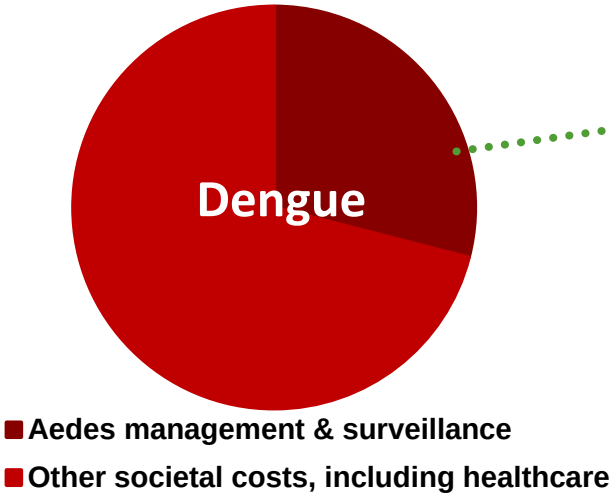
Zika

US$3.5 billion/year; microcephaly $4M/case[2]

Chikungunya

$80-160/case[3]; 2006 outbreak infected 1.5 million people in India[1]





Vector control is just a fraction of the total cost to affected communities

[1]World Health Organization 2017
[2]World Bank Group 2016
[3]Meason & Paterson 2014 *Health & Human Rights Journal*

Oxitec reduces mosquito populations

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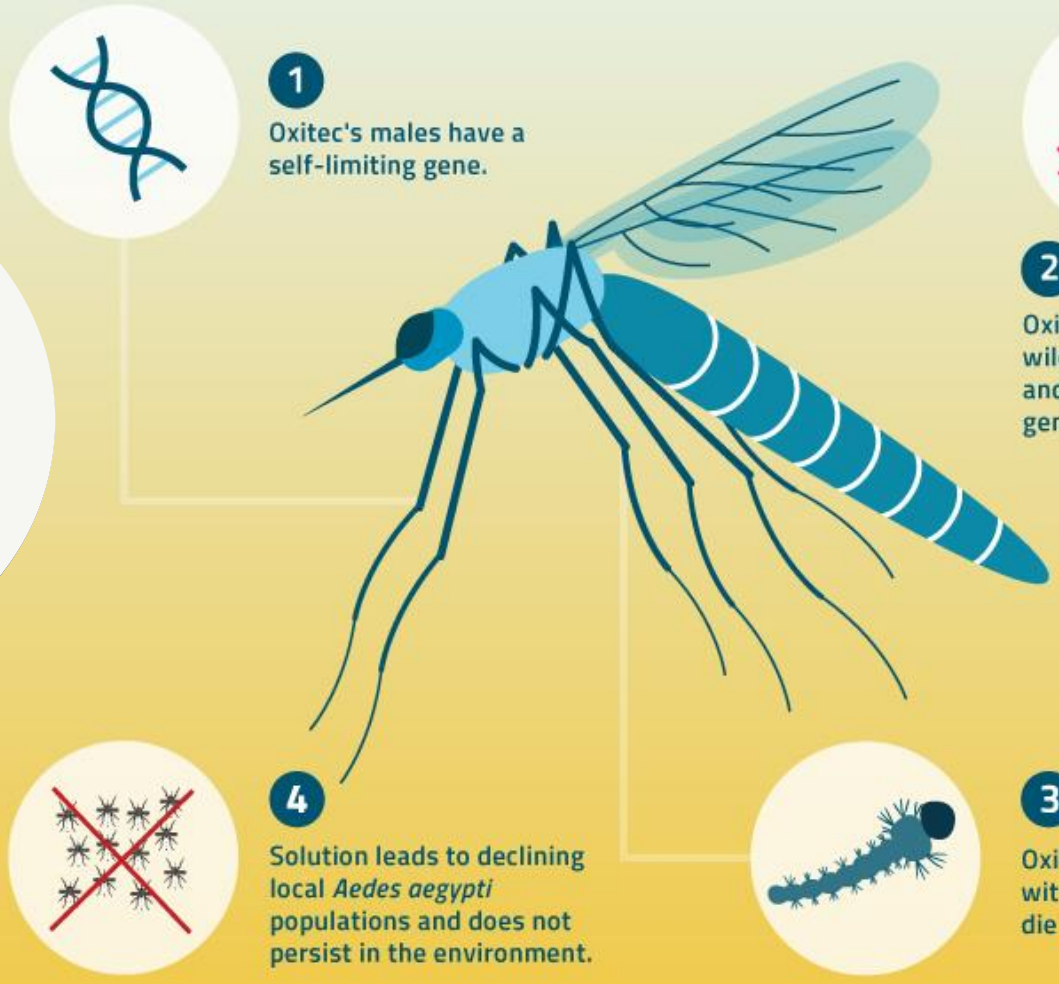
SELF-LIMITING GENE

HOW IT WORKS



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Oxitec OX513A

Inject genes into mosquito eggs

Self-limiting Gene

Fluorescent Marker Gene

Self-limiting Gene

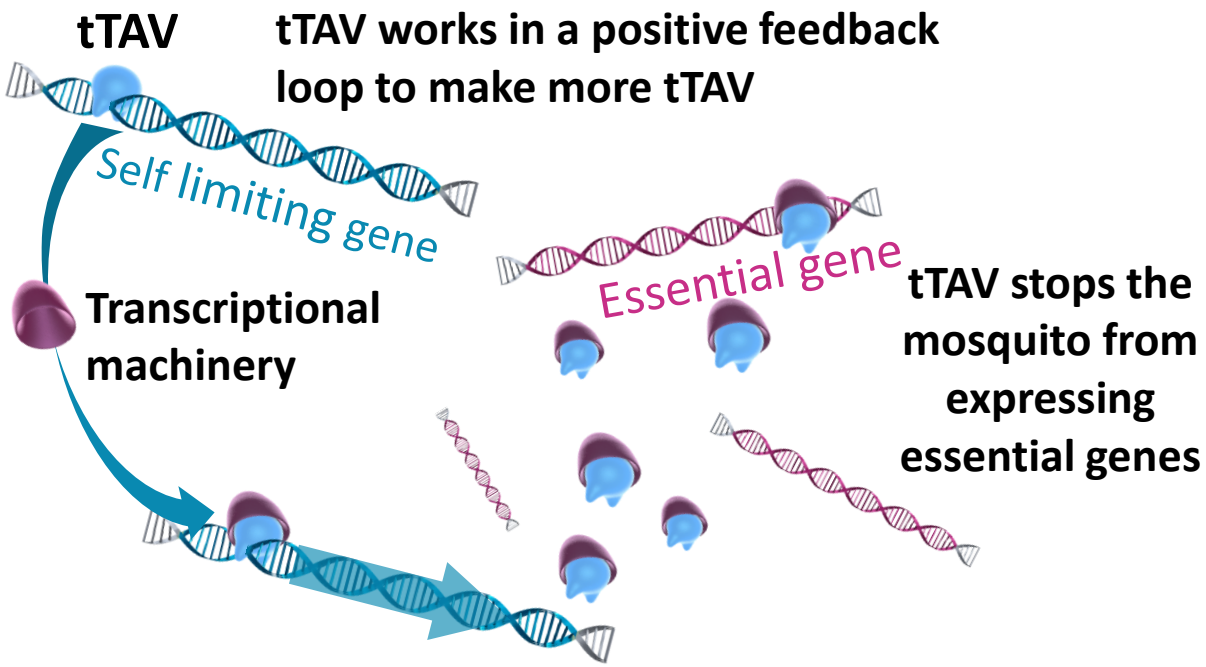
- **Inherited**: Offspring do not survive to adulthood
- After releases stop**, genes do not persist** in the environment
- Repressed with an **antidote** (tetracycline) during insect production

Fluorescent Marker Gene

Fluorescent protein detected by microscope

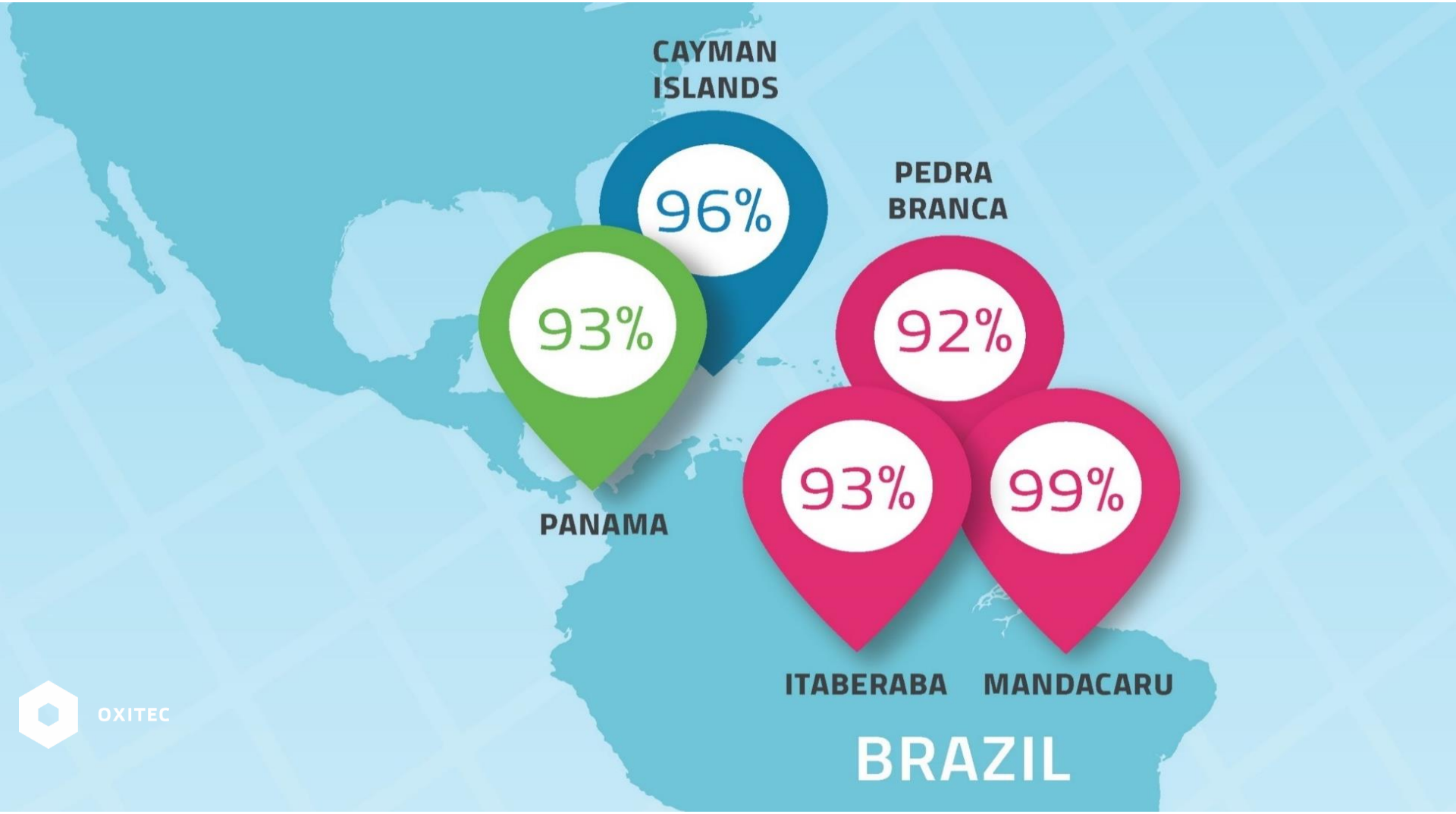
- Identifies **Oxitec insects vs. pest ones**
- Estimation of pest population sizes and **monitoring of suppression in real time**
- Releases can be adjusted based on tracking data

Self-limiting technology



Pest mosquito offspring die before they can reproduce

Field trials have consistent results



OX513A *Ae. aegypti* development

WORLD ECONOMIC FORUM

Technology Pioneer 2008

comissão técnica nacional

CTNBio de biossegurança

2002
OX513A created

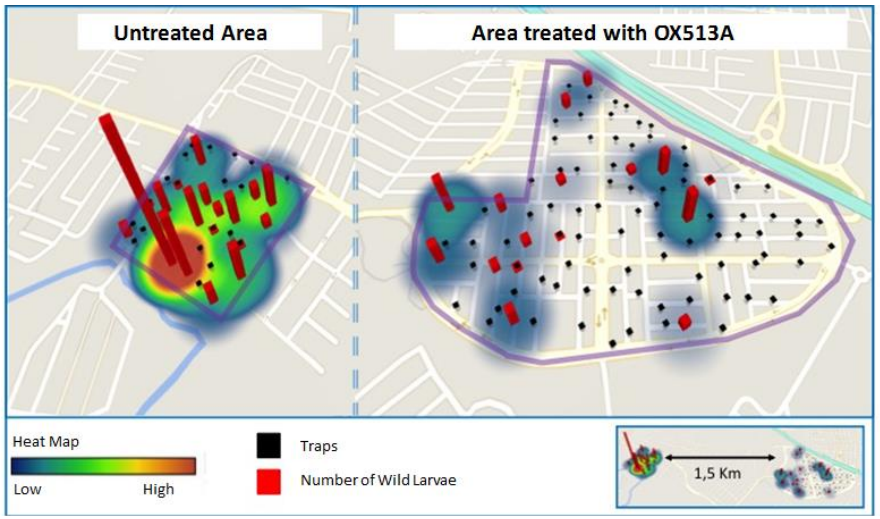
2009 -
Grand Cayman trial: 96% suppression

2010 -
Brazil
Three trials: All >90% suppression

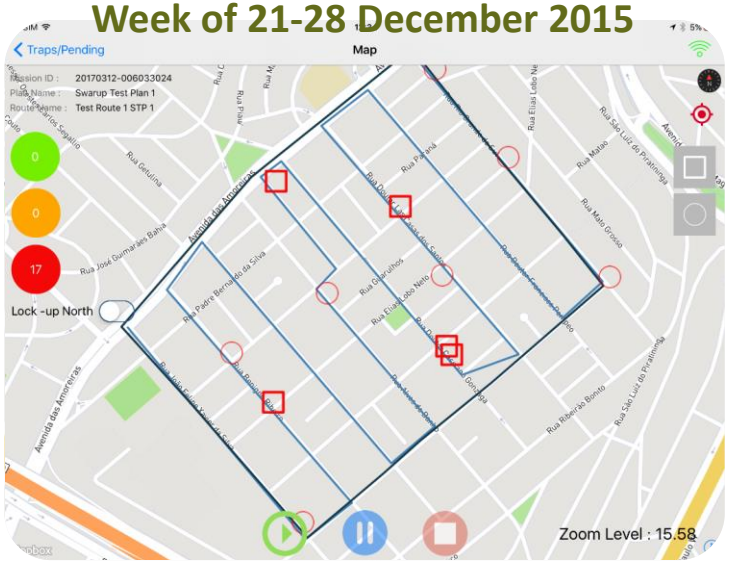
2014
Panama trial +
No *Ae. albopictus* niche replacement.
No persistence in the environment

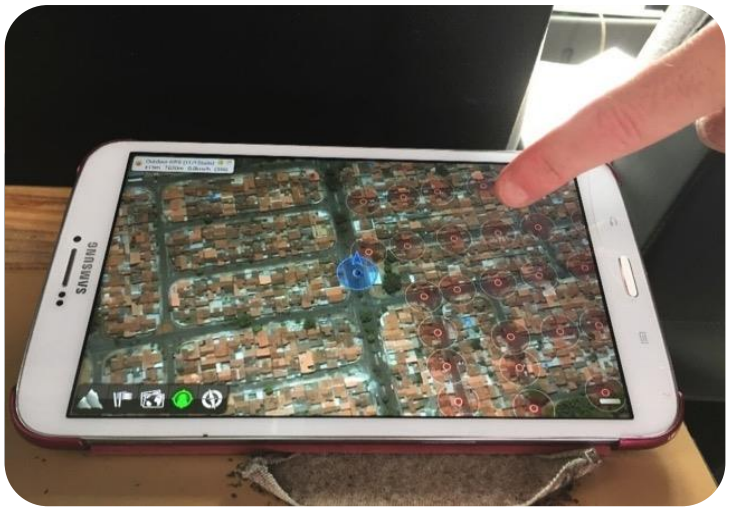
2014-2017
Brazil: CTNBio Approval, ANVISA announced they will issue a temporary registration
US: FDA Publish FONSI & EA
Global: WHO PAHO/CARPHA recommend pilot deployment under operational conditions
Piracicaba project (65,000 people)
Cayman project

Real time monitoring capability



Example: Infestation map CECAP/Eldorado
Week of 21-28 December 2015





Monitoring of eggs and the fluorescent marker allows

- Adaptive release
- Development of decision support systems

Oxitec added strengths

Targeted, cost-effective approach

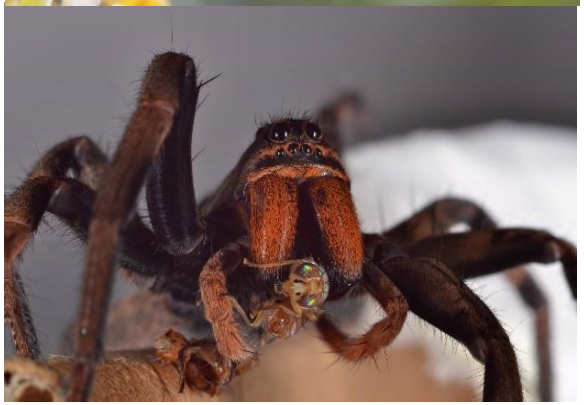
- Males actively seek females
- Effective with insecticide resistant insects
- No radiation: Lower costs, no effect on fitness
- Demonstrated field efficacy

Human safety

- Approved by regulators
- Male focused releases
- Fluorescent marker: track & trace
- Non toxic, non allergenic

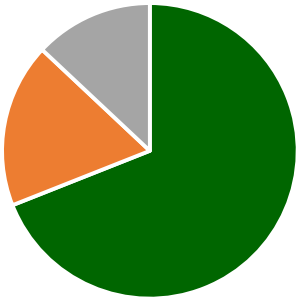
Environmentally benign

- No chemical residues
- No direct impact on non-target species
- Not persistent in the environment
- Built-in biosecurity

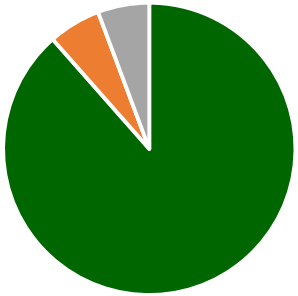


Consumer support

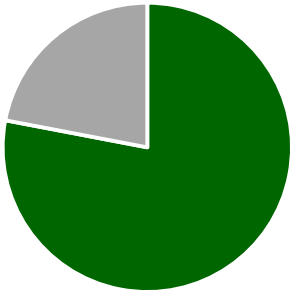
Cayman Islands



Piracicaba, Brazil



United States*



Monroe County referendum 2016 : 31 of 33 precincts voted in favour of trialling Oxitec's solution

Product Portfolio

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Agriculture

Target	Crop
 **Medfly** *Ceratitis capitata*	Citrus/pome/ stone fruit
 **Olive fly** *Bactrocera oleae*	Olive
 **Diamondback Moth** *Plutella xylostella*	Brassica
 **Pink Bollworm** *Pectinophora gossypiella*	Cotton
 **Fall armyworm** *Spodoptera frugiperda*	Broadacre

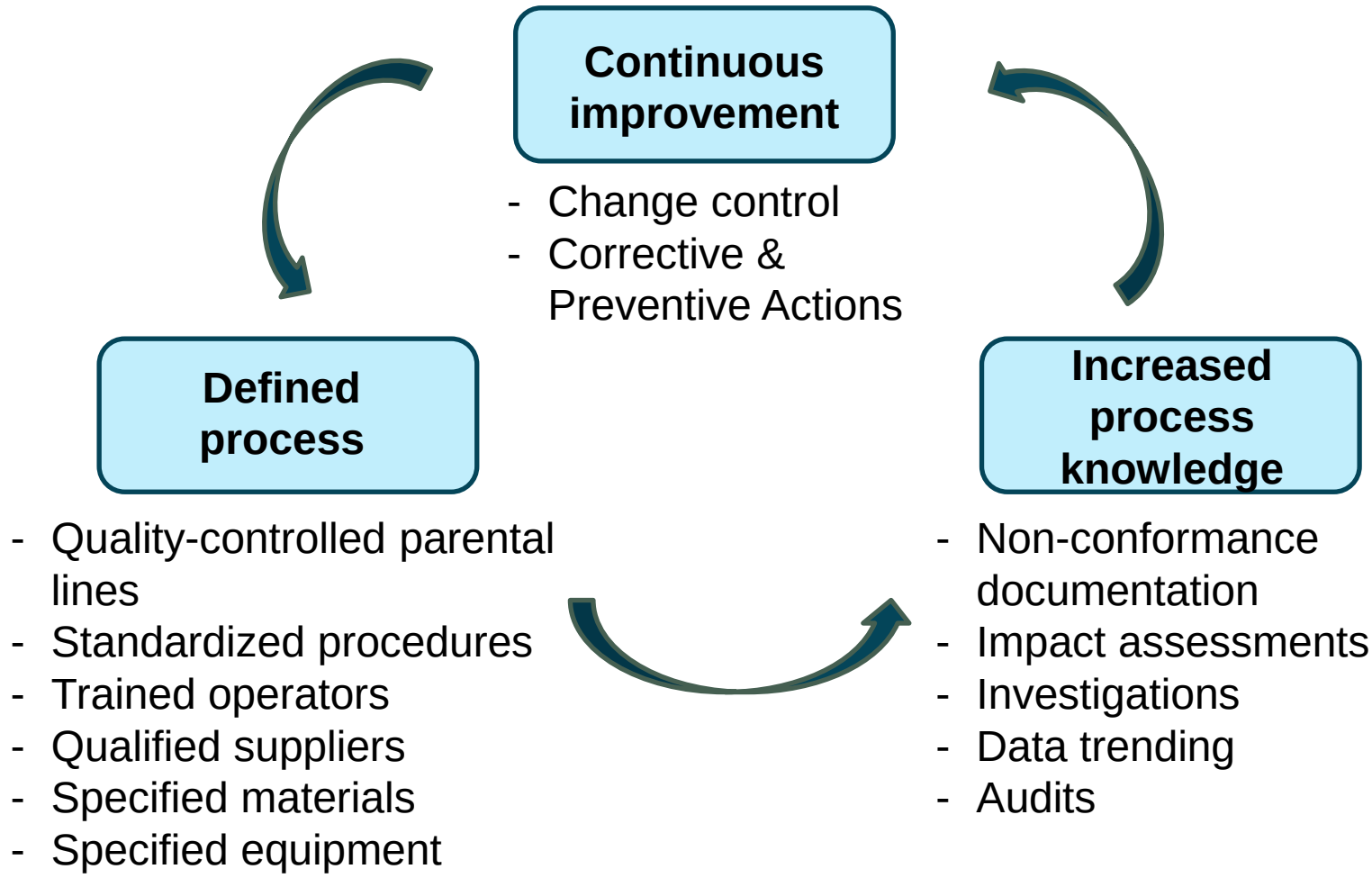
Public Health

Target	Vector of
 **Mosquito** *Aedes aegypti*	Dengue, Zika, & Chikungunya
 **Mosquito** *Aedes albopictus*	Dengue, Zika, & Chikungunya

In development

Target	Attacks
 **Fruit fly** *Drosophila suzukii*	Soft fruit

Quality Management System



New factory in Piracicaba, Brazil

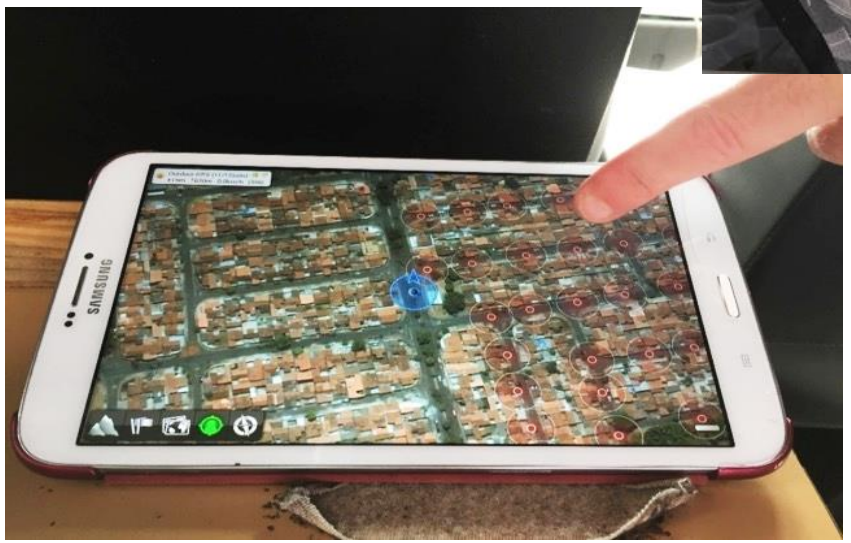
54,000 square feet, capacity of 60 million Oxitec males per week

Operations – egg production

Operations – Pupae production

Operations – adult production

Operations – adult release

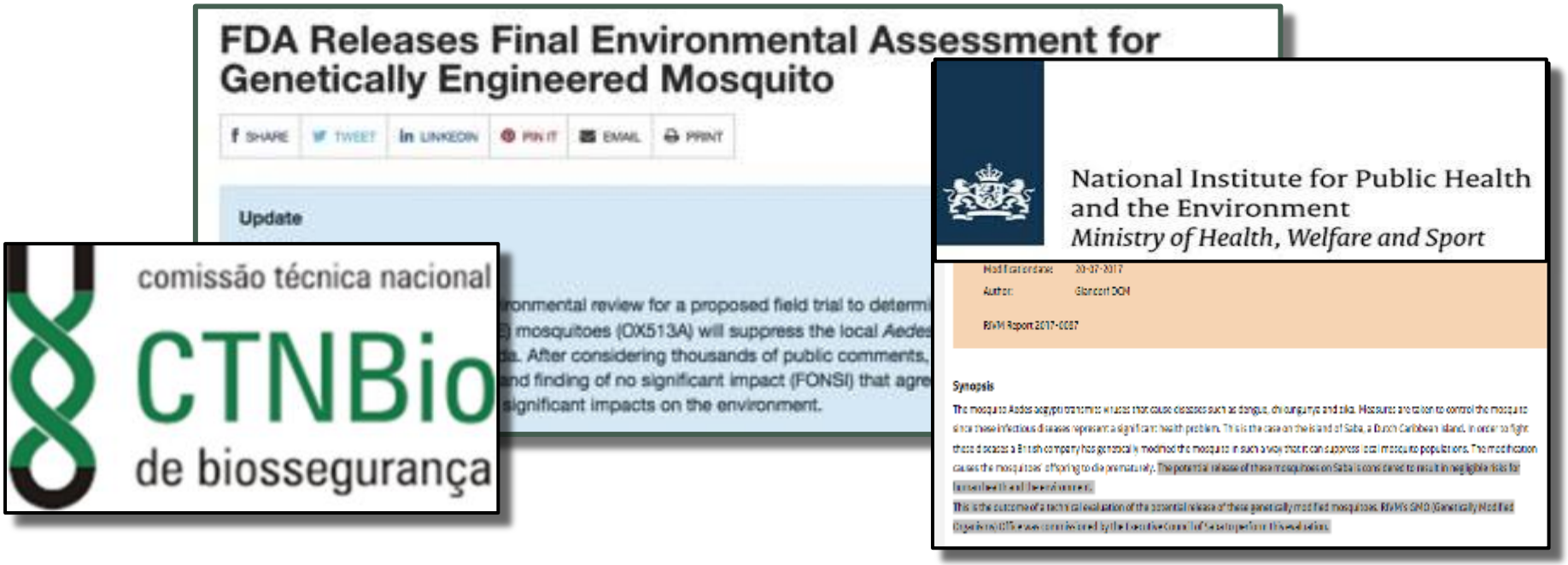


Brazil – expanding the program

- Purple – 35 – 65,000 people, 13 km^2
- Red – treated area, ~5000 human pop, ~ 50 Ha
- Yellow – untreated control sites

2. Overview of regulatory assessments and decisions

Recent regulatory opinions, OX513A



Recent regulatory milestones for OX513A

April 2014	August 2016	June 2017
Brazil's CTNBio granted approval for commercial release	**FDA publishes final FONSI and environmental assessment for trial in Florida Keys**	**National Conservation Council of The Cayman Islands approved territory-wide operational use**

EU publications for OX513A

June 2017	July 2017
French High Council of Biotechnology recognizes the potential for use in French territories	**GMO office of the Dutch National Institute for Public Health and the Environment (RIVM)** ***Positive evaluation of potential***

Risk assessment analysis

- Identification of potential hazards and exposure pathways
- Characterisation of potential hazard
- Characterisation of potential /plausible exposure pathway
- Estimation of risk
- Risk management strategy
- Risk conclusion

Key regulatory opinion

Year	Country	Regulatory body granting approval/positive opinion	Approval /positive opinion
2010	Brazil	Comissão Técnica Nacional de Biossegurança (CTNBio)	Approval for open field release
2010	Malaysia	Genetic Modification Advisory Committee (GMAC), Ministry of Natural Resources & Environment (NRE), Government of Malaysia	Approval for open field use
2009-2010	Cayman Islands	Ministry of Agriculture, Grand Cayman	Approval for open field use
2014	Brazil	Comissão Técnica Nacional de Biossegurança (CTNBio)	Approval for commercial release
2014	Panama	National Biosafety Commission Panama	Approval for open field use
2015	Cayman Islands	Ministry of Agriculture, Department of Environment Grand Cayman	Approval for open field use
2016	U.S.	United States Food and Drug Administration Center for Veterinary Medicine	Approval for open field use Environmental Assessment (EA) and Finding of No Significant Impact (FONSI)
2017	Netherlands	GMO office of the Dutch National Institute for Public Health and the Environment	Positive opinion on technical evaluation of a potential release of OX513A Aedes aegypti mosquitoes on the island of Saba
2017	France	France High Council for Biotechnology (HCB)	Positive opinion on the use of OX513A for vector control
2017	Cayman Islands	Cayman Islands National Conservation Council	Approval for operational use, territory wide in the Cayman Islands

Key assessment criteria

Agencies use science based risk assessment to inform decision making

Each country has assessed the potential harms to:

- ✓ human safety
- ✓ Non target organisms (NTOs)
- ✓ receiving environment

All regulatory submissions for OX513A have received approval for open release trails and programs: Brazil, Panama, Cayman, Malaysia, US

Submission formats to governments may vary but same core data; same objective

Overarching OX513A risk hypothesis

Oxitec's data shows that:

The environmental release of OX513A will cause no more harm to humans, NTOs and the environment, **than the existing *Aedes aegypti* population**

Overview of some regulatory decisions

Country decisions:

- 2014 Brazil CTNBio: Conclude that *Aedes aegypti* poses **no additional risks** to the environment, human beings and animals
- 2016 FDA: OX513A is **not expected to cause any significant adverse impacts** on the environment or human and non-target animal health beyond those caused by wild-type mosquitoes
- 2017 RIVM:The potential release of these mosquitoes on Saba is considered to result in **negligible risks** for human health and the environment

3. Summary of data provided to support regulatory assessments and decisions

Commonly required information

- ✓ Characteristics of
  - ➢ recipient insect
  - ➢ donor organisms
  - ➢ Vector
  - ➢ Genetic modification
- ✓ Survival, multiplication, dispersal and conditions affecting these parameters in the environment
- ✓ Information relating to intended use
- ✓ Interactions with other organisms in the environments
- ✓ Detection methods of the GM insect
- ✓ Receiving environment
- ✓ Risk assessment (human safety, NTOs, receiving environment)

Evidence/data provided to support negligible risk to Human and NTOs

Potential impacts on human or NTOs (not an exhaustive list)	Evidence/Data provided (not an exhaustive list)
Toxic /allergenic effects in humans or nontarget organisms	Bioinformatics: Lack of toxic and allergenic potential Proteins below LOD in OX513A mosquito saliva :immunological response no different to the bites from wild type Feeding studies on predator species (toxyrinchites and guppy fish) fed a diet exclusively comprised of OX513A larvae showed no adverse effects
Increase in transmission of other diseases transmitted by mosquitoes	Males are released which do not bite or transmit disease Less than 0.2% OX513A females may be co-released or are present as a result of incomplete penetrance but they have a relatively short lifespan and lifespan is considerably shorter than the EIP required for viral development
Transfer of the rDNA construct	the rDNA construct is stably integrated in the mosquito genome and is incapable of being transferred through sexual means

Evidence/data provided to support negligible risk to human and NTOs

Potential impacts on human or NTOs safety (not an exhaustive list)	Evidence/Data provided (not an exhaustive list)
Increase in population of other mosquitoes that may contribute to increase of diseases	A suppression field trial showed suppression of *Ae. Aegypti* without an increase in Ae. Albopictus at the same site demonstrating that release of OX513A does not lead to an increase in other mosquito species
Failure of the introduced traits	Stability of the inserted rDNA construct has been confirmed for over 120 generations; in the unlikely event that the introduced lethality trait is comprised, OX513A mosquitoes would be functionally no different and no fitter than the wild ones.

Evidence/data provided to support negligible risk to the environment

Potential impacts on the environment (not an exhaustive list)	Evidence/Data provided (not an exhaustive list)
Interbreeding with related mosquito species	Biological data from experiments conducted and literature shows that cross-species mating results in non-viable progeny; Mating in mosquitoes is very species specific
Gene persistence	After releases stop, genes do not persist in the environment
Establishment of OX513A in the environment	Self limiting trait demonstrated; More than 95% progeny die before reaching viable adulthood in absence of tetracycline; environmental levels of tetracycline too low to allow survival
Development of resistance to insecticides in the local population of *Ae. aegypti*	Laboratory studies shown that OX513A are susceptible to insecticides used for mosquito control.

Evidence/data provided to support negligible risk to the environment

Potential impacts on the environment (not an exhaustive list)	Evidence/Data provided (not an exhaustive list)
Effect on parasitoids	No specific parasitoids are known to be associated with *Aedes aegypti*
Effect on predators	Feeding studies on predator species (toxorhynchites and guppy fish) fed a diet exclusively comprised of OX513A larvae showed no adverse effects
Effect on flora	There is no evidence that *Ae. Aegypti* is a pollinator for any plant species; not a plant pest

>14 years of studies - biosafety profile

- Genetically and phenotypically stable; >120 generations since 2002
- No toxic or allergenic components used - bioinformatics
- No harm to predators
  - Two oral exposure studies available
- Lifespan 2-4 days in environment
  - Males do not bite or transmit disease
  - No genetic components in saliva
- Fully susceptible to insecticides
- Species-specific mating
- No environmental establishment
- Robust environmental monitoring methods
- Female vector competence not increased

- **No unmanageable risks identified by regulators to date**
- **Confirmed safety profile**

Risk assessment analysis

- Identification of potential hazards and exposure pathways
- Characterisation of potential hazard
- Characterisation of potential /plausible exposure pathway
- Estimation of risk
- Risk management strategy
- Risk conclusion

Thank you

Back-up slides

Genotype verification

- The sequence of the construct in OX513A is as intended without re-arrangements.
- The insertion is not known to disrupt endogenous gene function and no proteins other than those intended are likely to be produced
- Vector backbone sequences from the plasmid used for transformation, including antibiotic resistance genes or origins of replication, have not been detected by molecular analysis.
- No contaminating materials were introduced during the transformation process
- The non-autonomous transposable element used in the transformation is stable under a wide variety of conditions
- The insert has been shown to be stable and a complete single copy insertion
- No sequences have been inserted that encode for pathogens, toxins, or allergens
- The expression pattern of the inserted trait is as expected for a single insertion event
- Regular genotyping of the OX513A colony, and quality assurance procedures have showed that the genotype has been consistently maintained