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Change in Regulation is Necessary for Genetically Engineered Mosquitoes

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CHANGE IN REGULATION IS NECESSARY FOR GENETICALLY ENGINEERED MOSQUITOES

*Insung Hwang**

ABSTRACT

Millions of genetically engineered (GE) mosquitoes could soon be released in Key West, Florida as an effort to eradicate wild mosquitoes that are transmitters of diseases such as malaria, dengue, and chikungunya. Both international and domestic regulations fail to provide effective regulatory schemes that can facilitate the application of this technology while ensuring all safety and environmental aspects are properly addressed. The Food and Drug Administration's assertion of jurisdiction is based on its assessment that the GE mosquitoes are "animal drugs" under the Federal Food, Drug, and Cosmetic Act. This is especially troublesome because the end goal of using these mosquitoes is to prevent diseases in humans, which are not "animals" under the statute. Also, the current scheme only regulates the engineered gene inside the mosquito, but not the mosquito itself, and fails to account for the fact that the mosquito is a living animal that acts separately and independently from the engineered gene inside. Moreover, the U.S. Department of Agriculture's voluntary abrogation of jurisdiction is questionable because it had asserted jurisdiction on other GE insects and accumulated extensive experience in dealing with such issues. Instead, Mexico's approach of establishing a separate federal-level regulatory body specifically for genetically modified organisms could be instructive. No matter what the solution, some change in regulation addressing GE mosquitoes has become even more urgent with the recent spread of Zika virus in the U.S.

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I. MILLIONS OF GENETICALLY ENGINEERED (GE) MOSQUITOES TO BE RELEASED IN FLORIDA

Oxitec, a British biotech firm launched by Oxford University researchers, is preparing to release millions of genetically engineered (GE) mosquitoes in Key West, Florida.¹ Oxitec has developed and patented genetic engineering technology to breed *Aedes aegypti*, yellow fever mosquitoes, “with fragments of proteins from the herpes simplex virus and *E. coli* bacteria as well as genes from coral and cabbage.”² This technology produces mosquitoes containing a “self-limiting” gene.³ Unlike female mosquitoes, male mosquitoes with the self-limiting gene only feed on nectar and do not bite.⁴ When released into the wild, those males could breed with female mosquitoes to produce offspring that would inherit the self-limiting gene that is activated and kills mosquito larvae before they can fly or bite, thus decreasing the total population of biting mosquitoes in the environment.⁵

The rationale for engaging in this extraordinary scientific endeavor is simple and reasonable: reducing disease transmission.⁶ “Of all disease-

1. Jennifer Kay, *Millions of GMO Insects Could be Set Loose in Florida Keys*, ASSOCIATED PRESS (Jan. 25, 2015 1:22 AM), <http://www.bigstory.ap.org/article/078caa7e75df442295e8c3db634fe9af/millions-gmo-insects-could-be-set-loose-florida-keys>.

2. *Id.*

3. See Oxitec, *How It Works*, AGRICULTURE, <http://www.oxitec.com/health/how-it-works> (last visited Dec. 21, 2016).

4. *See id.*

5. *Id.*

6. Oxitec, *Overview*, OUR SOLUTION, <http://www.oxitec.com/our-solution/> (last visited Dec. 21, 2016).

transmitting insects, the mosquito is the greatest menace.”⁷ Mosquitoes carry and transmit fatal diseases such as malaria, dengue, and chikungunya.⁸ These diseases alone cause several million deaths and there are hundreds of millions of new cases every year.⁹ Over 2.5 billion people around the world are at risk of contracting malaria.¹⁰ In 2015, there were 212 million new cases of malaria, resulting in 429,000 deaths.¹¹ Dengue and chikungunya are infamous for inducing excruciating pain.¹² A recent study found that there were 390 million dengue infections annually, with approximately 96 million manifesting clinically.¹³ To make matters worse, there are no vaccines or cures for dengue or chikungunya.¹⁴

Mosquito-borne diseases have disproportionately grave impacts on children and the poor. Over one million children die every year from malaria.¹⁵ And despite the lack of a definitive relationship between poverty and dengue, mosquito-borne diseases bring grave economic impacts on countries, communities, and families by affecting the health and working capacity of hundreds of millions of poor people.¹⁶ Children miss school due either directly to contracting malaria or in order to serve as substitute labor for parents or siblings who have contracted it.¹⁷ Children in infected areas have an average of two to three bouts of malaria each year,¹⁸ making the disease one of the largest drivers of absenteeism among school children in affected areas, ultimately resulting in higher failure and drop-out rates.¹⁹

7. World Health Org. [WHO], *World Health Report: Executive Summary, Insect-borne Diseases* (1996), http://www.who.int/whr/1996/media_centre/executive_summary1/en/index9.html [hereinafter *World Health Report*].

8. *Id.*

9. *Id.*

10. WHO, *Vector-borne Diseases*, MEDIA CENTRE (Feb. 2016), <http://www.who.int/mediacentre/factsheets/fs387/en/>.

11. WHO, *Malaria*, MEDIA CENTRE, <http://www.who.int/mediacentre/factsheets/fs094/en/> (last updated Dec. 2016).

12. See WHO, *Chikungunya*, MEDIA CENTRE, <http://www.who.int/mediacentre/factsheets/fs327/en/> (last updated Apr. 2016); WHO, *Dengue and Severe Dengue*, MEDIA CENTRE, <http://www.who.int/mediacentre/factsheets/fs117/en/> (last updated July 2016).

13. WHO, *Dengue and Severe Dengue*, *supra* note 12.

14. *Id.*; WHO, *Chikungunya*, *supra* note 12.

15. See Healthy Environments for Children Alliance, *Issue Brief Series: Vector-borne Diseases*, WHO, <http://www.who.int/heca/infomaterials/en/vector-borne.pdf> (last visited Dec. 5, 2016).

16. Kate Mulligan et al., *Is Dengue a Disease of Poverty? A Systematic Review*, 109 *PATHOGENS AND GLOBAL HEALTH* 10, 10–18.

17. See Healthy Environments for Children Alliance, *supra* note 15.

18. See *id.*

19. See Jeffrey Sachs & Pia Malaney, *The Economic and Social Burden of Malaria*, 415 *NATURE* 680, 683 (2002).

Mosquito-borne disease is no longer a problem limited to the tropics. Global warming and ease of travel are threatening to spread the diseases farther away from the equator.²⁰ This endangers the southernmost U.S. communities, such as Key West, Florida.²¹ The recent outbreak of the Zika virus in a section of Miami Beach is a good example of how Florida is susceptible to mosquito-borne diseases that originate abroad.²²

Currently, one of the prevalent ways of controlling the mosquito population is insecticides, which are often applied door-to-door and from helicopters.²³ However, mosquitoes have grown immune to four of the six insecticides used to kill them in the Key West area.²⁴ Therefore, developing new ways of exterminating the mosquito population is absolutely necessary for the welfare of people living in Florida in order to minimize the risk of human exposure to mosquitoes carrying lethal viruses.

Even if we assume that society understands the need to implement groundbreaking technology to prevent its own exposure to deadly diseases, novel scientific endeavors that incorporate GE organisms tend to create a great deal of anxiety.²⁵ Although the overwhelming majority of the population of mosquitoes to be released in Florida is male, Oxitec admitted that a tiny percentage of the release batch would contain biting female mosquitoes.²⁶ The company claims that nothing will happen if a person is bitten by one of the stray female mosquitoes.²⁷ The company also says that the environment will not be impacted at all.²⁸ In an attempt to further ameliorate the public's anxiety, Oxitec stated that it will take responsibility if something goes wrong due to the company's actions or inactions.²⁹ Despite these assurances, various civil protests, including an online petition that has been signed by more than 150,000 people, have arisen in fear that Oxitec's application will be approved.³⁰

20. Daniel Chang, *Florida Reports Three More Mosquito-Borne Zika Infections in Miami Beach*, MIAMI HERALD (Oct. 5, 2016 4:01 PM), <http://www.miamiherald.com/news/health-care/article106200452.html>.

21. *Id.*

22. *Id.*

23. Kay, *supra* note 1.

24. *Id.*

25. See Lizette Alvarez, *A Mosquito Solution (More Mosquitoes) Raises Heat in Florida Keys*, N.Y. TIMES (Feb. 19, 2015), http://www.nytimes.com/2015/02/20/us/battle-rises-in-florida-keys-over-fighting-mosquitoes-with-mosquitoes.html?_r=0.

26. *Id.*

27. *Id.*

28. *Id.*

29. *See id.*

30. Mila de Mier, *Online Petition: Say No to Genetically Modified Mosquitoes Release in the Florida Keys*, <https://www.change.org/p/say-no-to-genetically-modified-mosquitoes-release-in-the-florida-keys> (last visited Dec. 21, 2016) [hereinafter *GE Mosquito Petition*].

Leaving aside the questions of safety and efficacy that lend themselves to scientific inquiry, the goal of this Note is to explore the regulatory mechanisms in place for approving Oxitec's technology, as well as the reasons why a change in regulation is necessary in order to better reflect the new technology. The Food and Drug Administration (FDA), in its preliminary Finding of No Significant Impact (FONSI), has already concluded that "the probability that the release of [GE] male mosquitoes would result in toxic or allergenic effects in humans or other animals is negligible."³¹ This meant that Oxitec still needed one additional approval from the Florida Keys Mosquito Control District (FKMCD) Board of Commissioners, which held two non-binding referendums regarding the proposed mosquito release for Key Haven and Monroe County residents on November 8, 2016.³² The results of the referendums were split: the Key Haven residents voted against the project while the broader Monroe County residents voted in favor.³³ Ultimately, the FKMCD board decided that the trials will not take place in Key Haven but will take place somewhere else in the Key still to be determined.³⁴

But the development of a safe technology does not require a healthy regulatory framework. The Obama administration stated that the regulatory scheme governing GE animals "had become outdated and confusing and did not foster public confidence."³⁵ While the government continues to prepare a new system, the emergence of new technologies such as the GE mosquitoes has exposed weak points of the current regulatory scheme. This Note addresses the gaps in that system, and proposes ways to improve the regulation of technologies involving genetically engineered organisms, such as the GE mosquitoes, that are designed to address human health risks.

31. FDA, PRELIMINARY FINDING OF NO SIGNIFICANT IMPACT (FONSI) IN SUPPORT OF AN INVESTIGATIONAL FIELD TRIAL OF OX513A Aedes Aegypti Mosquitoes (2016).

32. Florida Keys Mosquito Control District, *Latest Information on the Proposed Oxitec GM Mosquito Project*, GENETICALLY MODIFIED MOSQUITO, <http://keysmosquito.org/latest-gm-information/> (last visited Dec. 21, 2016).

33. Alexandra Sifferlin, *Genetically Modified Mosquitoes Divide Florida Residents*, TIME (Nov. 9, 2016), <http://time.com/4564304/genetically-modified-mosquitoes-divide-florida-residents>.

34. Greg Allen, *Florida Keys Approves Trial of Genetically Modified Mosquitoes to Fight Zika*, NPR (Nov. 20, 2016), <http://www.npr.org/sections/health-shots/2016/11/20/502717253/florida-keys-approves-trial-of-genetically-modified-mosquitoes-to-fight-zika>.

35. Andrew Pollack, *White House Orders Review of Rules for Genetically Modified Crops*, N.Y. TIMES (July 2, 2015), <http://www.nytimes.com/2015/07/03/business/white-house-orders-review-of-biotechnology-regulations.html> (summarizing John P Holdren et al., *Improving Transparency and Ensuring Continued Safety in Biotechnology*, WHITE HOUSE BLOG (July 2, 2015 2:57 PM), <https://obamawhitehouse.archives.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology>).

II. GE MOSQUITOES ARE MISCHARACTERIZED IN THE CURRENT DOMESTIC REGULATIONS

Domestic regulations do not sufficiently address many aspects of the GE mosquito technology. This section points out that the assertion of jurisdiction by the FDA over the GE technology based on the assessment that the GE mosquitoes are “animal drugs” under the Federal Food, Drug, and Cosmetic Act (FDCA) is a mischaracterization. This is because the end goal of using the GE mosquitoes is to prevent diseases in humans, not animals. That end goal might lead to the conclusion that GE mosquitoes qualify as drugs for humans. However, human treatment would put the GE mosquitoes under a different regulatory framework than animal drugs.³⁶ Also, the current scheme regulates the engineered gene inside the mosquito, but not the mosquito itself. This fails to account for the fact that the mosquito is a living animal that acts separately and independently from the engineered gene inside.³⁷ Finally, this section discusses that the GE mosquitoes are so different from traditional drugs that they might necessitate the consideration of extra-label use.³⁸

A. *GE Mosquitoes Are Regulated as “Animal Drugs” Under the Federal Statute But Are Actually Human Drugs*

Currently, the FDA asserts jurisdiction over the GE mosquitoes because a genetic modification through introduction of recombinant DNA (rDNA) in animals is classified as a “new animal drug” under of the FDCA, the authorizing statute for the FDA.³⁹ A “new animal drug,” under Section 201(v) of the Act, is “any drug intended for use for animals other than man,” for which the safety and efficacy has not been sufficiently proven.⁴⁰ “Drug” is defined in Section 201(g)(1)(C), which includes “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”⁴¹ The FDA’s interpretation of its authority over genetically engineered animals through the statute is addressed in its Guidance for Industry document released in June 2015.⁴² The FDA’s justification for asserting its authority is that genetic engineering techniques are “intended

36. See *infra* Section II.A.

37. See *infra* Section II.B.

38. See *infra* Section II.C.

39. Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301–399f (2012).

40. *Id.* § 321(v).

41. *Id.* §321(g)(1)(C).

42. FDA, GUIDANCE FOR INDUSTRY #187: REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS, 5–9 (2015) [hereinafter FDA GUIDANCE].

to affect the structure or function of the body of the GE animal.”⁴³ Therefore, according to the FDA, the genetic engineering method used in the GM mosquitoes is within its jurisdiction provided by the FDCA.

The self-limiting gene does indeed “affect the structure or any function of the body” of the mosquito. The male mosquitoes that are genetically modified in the lab to be released into the wild cannot reach maturity unless tetracycline is present.⁴⁴ Scientists artificially feed GE mosquito larvae with the tetracycline “antidote” in the lab, allowing those mosquitoes to survive until they are able to mate with female mosquitoes in the wild.⁴⁵ However, not enough tetracycline is available in the natural environment, so the offspring that inherit the self-limiting gene die off naturally.⁴⁶

However, a regulatory mischaracterization of the GE mosquitoes reveals itself when one considers the other intended purpose of the self-limiting gene—limiting human exposure to tropical diseases. Section 201(g)(1)(B) of the FDCA provides another definition of the term “drug” as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.”⁴⁷ The intention to minimize humans’ exposure to tropical diseases might qualify as a “prevention of disease” under this definition in the FDCA. If that interpretation of the statute holds, then the issue of GE mosquitoes would no longer be confined to the realm of animal drugs.

Drugs for human use are regulated under a different section of the FDCA. Using that paradigm, jurisdiction for drug approval would belong to the Center for Drug Evaluation and Research (CDER) / Center for Biologics Evaluation and Research (CBER) instead of the Center for Veterinary Medicine (CVM).⁴⁸ In fact, some organizations and individuals such as Friends of the Earth (FOE) have asserted that “[t]he release of GE mosquitoes as an attempt to curb the spread of disease should be considered a medical trial and must follow the strict laws and guidelines in place to protect human subjects in medical trials.”⁴⁹

43. *Id.* at 6.

44. Oxitec, *The Science*, OUR SOLUTION, <http://www.oxitec.com/our-solution/technology/the-science/> (last visited Dec. 21, 2016).

45. *Id.*

46. *Id.*

47. 21 U.S.C. § 321(g)(1)(B) (2012).

48. FDA, *How Drugs are Developed and Approved*, DRUGS, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved> (last visited Jan. 21, 2017); FDA, *About CBER*, ABOUT FDA, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123340.htm> (last visited Jan. 21, 2017).

49. Friends of the Earth, *Issue Brief: Genetically Engineered Mosquitoes in the U.S.*, http://www.foe.org/system/storage/877/df/1/959/Issue_brief_GE_mosquitoes_in_U.S.pdf (last visited Dec. 21, 2016).

In an attempt to interpret the scope of the term “drug” under the FDCA, the Court of Appeals for the D.C. Circuit found that “the crux of FDA jurisdiction over drugs lay in manufacturers’ representations as revelatory of their intent.”⁵⁰ The Second Circuit has also found that “[t]he vendors’ intent in selling the product to the public is the key element in this statutory definition.”⁵¹ This intent is “determined by [the vendors’] expressions or may be shown by the circumstances surrounding the distribution of the article.”⁵² Applying these rules to Oxitec’s project, there is no doubt that the mosquitoes are within the meaning of “drug” under the FDCA. Oxitec promotes its technology as providing “a proven means of protecting people from *Aedes aegypti* and the diseases it spreads,” which is a clear representation of the company’s intent to sell the GE mosquitoes as articles that benefit the public health.⁵³

It remains unresolved whether an article that serves its purpose without requiring direct contact with the human body can be considered a drug. The FDCA’s scope regarding its definition of “drug” has been interpreted broadly by courts in some instances. For example, the District of D.C. has categorized balloons containing laughing gas (nitrous oxide) sold in a parking lot at a rock concert as “drugs” because the defendant intended to sell a “mind-altering” article that affects the structure or function of the body.⁵⁴ Meanwhile, other courts have construed the term more narrowly. For example, the Second Circuit, in a per curiam opinion, affirmed the position of the lower court that it would be absurd to interpret the statute literally when applied to cigarettes, since “any article which, used in the manner anticipated by the manufacturer thereof, comes into contact with any of the senses may be said to be an article ‘intended to affect the functions of the body of man.’”⁵⁵ That court reviewed the legislative history of FDCA to reach the conclusion that “Congress, had the matter been considered, would not have intended cigarettes to be included [as a drug].”⁵⁶

When defining “drug” in 1938, Congress could not possibly have foreseen that the statute would reach genetic engineering technologies that prevent human diseases without requiring any direct contact with humans. Rather than hypothesizing what Congress would have done in this circumstance, it is more relevant to consider GE mosquitoes in light of courts’

50. *Action on Smoking & Health v. Harris*, 655 F.2d 236, 238–39 (D.C. Cir. 1980).

51. *Nat’l Nutritional Foods Ass’n. v. Mathews*, 557 F.2d 325, 333 (2d Cir. 1976).

52. 21 C.F.R. § 201.128 (2016).

53. Oxitec, *Overview*, *supra* note 6.

54. *United States v. Travia*, 180 F. Supp. 2d 115, 118–19 (D.D.C. 2001).

55. *FTC v. Liggett & Myers Tobacco Co.*, 108 F. Supp. 573, 576 (S.D.N.Y. 1952), *aff’d*, 203 F.2d 955 (2d Cir. 1953).

56. *FTC v. Liggett & Myers Tobacco Co.*, 108 F. Supp. at 577.

analysis of whether *in vitro* diagnostic methods that do not come into direct contact with the human body are “drugs” under the FDCA.

Two seminal cases reach opposite conclusions on *in vitro* diagnostic methods. The first case, decided by the Supreme Court, involved an antibiotic sensitivity disc that comes in contact with cultures of a patient’s virus *in vitro* and screens for the optimal antibiotic to administer to patients by checking the sensitivity of the patient’s virus to a particular antibiotic.⁵⁷ The Court explained that “the disc is used, in conjunction with a patient’s specimen, in laboratory work exclusively, and never comes in contact with any part of the patient’s body itself.”⁵⁸ Despite that mechanism, the Court decided that the disc is indeed a “drug” under the FDCA because “the patient will tend to derive less benefit and perhaps some harm from a particular antibiotic if, though the drug itself was properly batch-tested, it was not the proper antibiotic to use” and that “Congress fully intended that the Act’s coverage be as broad as its literal language indicates.”⁵⁹

Contrarily, the District of New Jersey in 1975 held that an *in vitro* pregnancy kit is not a drug.⁶⁰ The pregnancy kit worked by reacting fresh urine with solutions contained in bottles provided in the kit.⁶¹ The court emphasized that “[t]his test is in glass, outside the body, using body fluids available by ordinary bodily processes (i.e., ‘*in vitro*’ to use the technical term). The test does not involve the injection or ingestion of any material in the human body itself (i.e., ‘*in vivo*’).”⁶² The court decided that the pregnancy test kit is not a “drug” under the FDCA because pregnancy is not a disease, rather it is a “normal physiological function of all mammals.”⁶³ The pregnancy kit, the court stated, is distinguishable from the antibiotic sensitivity disc case because the latter has “life-and-death risks involved in achieving a correct diagnosis.”⁶⁴

Neither case discussed the intended use of “prevention” delineated in the definition of “drug” under the FDCA; both focus on “diagnosis” and “treatment.” However, the District of New Jersey failed to address the possibility of using pregnancy test kits as a prevention measure. By allowing women to find out whether they are pregnant at an early stage of pregnancy, they can protect not only their own health, but also that of the fetus. Perhaps the court did not address this question because there was no cir-

57. See *United States v. Article of Drug Bacto-Unidisk*, 394 U.S. 784, 784 (1969).

58. *Id.* at 787.

59. *Id.* at 798–99.

60. *United States v. Article of Drug-Ova II*, 414 F. Supp. 660, 665 (D.N.J. 1975).

61. *Id.* at 663.

62. *Id.*

63. *Id.* at 664.

64. *Id.*

cumstantial evidence that showed the pregnancy test kit manufacturer intended to market or promote the product for that purpose. Or, maybe there was lack of proximity between the explicit use of the pregnancy test kit, which is merely checking for pregnancy, and the implied intended use for prevention of health risks.

As can be seen from the two decisions, a diagnostic method could be categorized as a “drug” under the FDCA regardless of whether it involves direct contact with the human body—the crucial point is how broadly the definition is interpreted. However, the District of New Jersey’s distinction, that the pregnancy kit does not provide an assessment of life-and-death risks, bolsters the FDA’s interpretation that the GE mosquito is not a drug for humans. Even though the purpose of the GE mosquito project is to save lives by preventing diseases, the project is not dealing with matters as urgent as checking the antibiotic sensitivity of patients who have already contracted serious diseases and whose lives depend on the results of the sensitivity test. That lack of urgency might only provide a weak proximity link between the release of the GE mosquitoes and the eventual intended consequences of the release—to prevent human disease.

Exactly how much urgency is necessary for a product to qualify as a drug under the “prevention” clause of the FDCA has not been settled. Therefore, although Oxitec announced that the intended use of the GE mosquitoes is to prevent human diseases, there might be lack of proximity between the release of the mosquitoes and the intended consequences of preventing humans’ exposure to diseases to say for certain that the FDA’s interpretation of the statute regarding the project is arbitrary and capricious under the Administrative Procedure Act.⁶⁵

B. FDA Fails to Account for Self-Acting Nature of Mosquitoes

Once the GE mosquitoes are released into the wild, they behave based on their own survival instinct, independent from the inserted gene. The self-limiting gene is not able to do its job unless the mosquito survives in the wild, pursues mating, and produces offspring. Not only is the success of Oxitec’s technology dependent on the function of the self-limiting gene, but it is also dependent on the capability of the lab-grown mosquitoes to survive and mate in the wild. In this sense, the GE mosquitoes are “self-acting.”

The self-acting GE mosquitoes, like the self-limiting genes inside them discussed in Section II.A. above, have two intended uses: decreasing the overall mosquito population and limiting human exposure to disease trans-

65. 5 U.S.C. § 706 (1966).

mitted by the mosquito.⁶⁶ The mosquitoes themselves are likely “drugs” under Section 201(g)(1)(C) of the FDCA because the decrease of the mosquito population is achieved by passing the self-limiting gene to offspring, which in turn affects the “function of the body” of the offspring by killing it.⁶⁷ Under this interpretation, the mosquito itself should be regulated under a separate layer of regulation from the self-limiting gene, or a new regulation scheme would have to be devised to both regulate the self-limiting gene and the mosquito itself simultaneously as a “new animal drug.”

However, a potential quandary that arises from the authorizing statute is that the self-limiting gene is a “drug” under the definition of the word in the statute, but the mosquito itself is not a “drug.” This confusion becomes especially important if we are to recognize the self-acting characteristics of GE mosquitoes. If we assume that the mosquito is a living animal that acts separately and independently from the self-limiting gene inside, then it is improper to assume that regulating the gene as a drug has the same effects as regulating the mosquito that contains the gene.

Comparing the GE mosquito technology to traditional drugs, the current regulation might treat the self-limiting gene as the chemical compound and the mosquito as the capsule, syringe, or other medium in which the drug is transported and delivered. The biggest failure of this analogy comes from the fact that a capsule or a syringe does not have self-acting characteristics, while a living, autonomous mosquito does. The current regulatory scheme does not account for this failure of analogy.

The closest thing to an explanation that the FDA has given regarding this issue is on its website’s Q&A page. There, the FDA states that “GE animals are not drugs” and explains that:

[The FDCA] defines a new animal drug as “an article (other than food) intended to affect the structure or any function of the body of . . . animals.” A recombinant DNA (rDNA) construct intended to affect the structure or function of an animal meets the definition of a new animal drug, regardless of whether the resulting GE animals are intended for food, or to produce pharmaceuticals or any other substances. As a short hand we sometimes refer to regulation of the article in such GE animals as regulation of the GE animal.⁶⁸

66. Oxitec, *Overview*, *supra* note 6.

67. See 21 U.S.C. § 321(g)(1)(C) (2012).

68. FDA, *General Q&A*, ANIMAL & VETERINARY, <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm113605.htm> (last updated Nov. 19, 2015).

Going back to the analogy to traditional drugs, the FDA's explanation essentially means that the compound inside the capsule is a drug while the capsule itself is not a drug, and the regulation of the compound inside the capsule is sufficient for the regulation of the capsule.

Perhaps the FDA made this statement because the agency wanted to make clear that a separate process is needed to approve additional products derived from GE animals that are intended to affect humans or other animals. For example, one of the intended purposes of creating GE animals is "to produce products intended for human therapeutic use (e.g., pharmaceutical products or tissues for transplantation; these GE animals are sometimes referred to as 'biopharm' animals)."⁶⁹ Instead of allowing the commercial use of therapeutics derived from GE animals by getting an approval just for the rDNA construct inside the GE animal, the FDA probably intended such producers to file a separate application for the approval of those therapeutics.⁷⁰ Applying it to the compound and capsule analogy above, the FDA might have wanted to say that approval of the compound inside the capsule does not mean that any other compound produced by the capsule itself is also approved.

However, this possible interpretation of the FDA's intention fails because no guidance is given for situations where the GE animal itself is used as a drug. The Center for Veterinary Medicine (CVM) department of the FDA, the GE animal application oversight body, offers six intended purposes for creating GE animals:

- (1) to enhance production or food quality traits (e.g., pigs with less environmentally deleterious wastes, faster growing fish);
- (2) to improve animal health (e.g., disease resistance);
- (3) to produce products intended for human therapeutic use (e.g., pharmaceutical products or tissues for transplantation; these GE animals are sometimes referred to as "biopharm" animals);
- (4) to enrich or enhance the animals' interactions with humans (e.g., hypo-allergenic pets);
- (5) to develop animal models for human diseases (e.g., pigs as models for cardiovascular diseases); and
- (6) to produce industrial or consumer products (e.g., fibers for multiple uses).⁷¹

None of these intended purposes include creating a GE animal to kill other animals or to mitigate humans' exposure to diseases, nor do any of the other

69. FDA GUIDANCE, *supra* note 42, at 4.

70. *Id.*

71. FDA, GUIDANCE FOR INDUSTRY: REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS (2015).

guidelines published by the FDA address the possible use of a GE animal as a drug for humans or other animals.⁷²

In fact, a double regulatory scheme, in which the rDNA inserted into a GE animal is regulated separately from a product derived from the GE animal, is already in place for any use of the GE animal currently conceived by the FDA that comes in contact with humans. In a guidance document for therapeutic products for human use derived from transgenic animals, the FDA states that “[t]he majority of products for human use derived from transgenic animals and intended for diagnostic, preventative or therapeutic purposes will be regulated as biological products.”⁷³

For example, in the case of xenotransplantation applications of GE animals, in which live organs, tissues, or cells from the GE animal are transplanted into the human body, the FDA “will regulate most xenotransplantation products as biological products. CBER regulates biological products, including cellular therapies, under authority of section 351 of the PHS Act (42 U.S.C. 262), and the [FDCA] (21 U.S.C. 321 et seq.).”⁷⁴

Meanwhile, no such double regulatory scheme exists for GE animals that are self-acting and come in direct contact with humans. It is possible that the FDA did not foresee that a GE animal could be used as a drug by itself. However, the lack of explicit guidance by a government agency regarding a particular subject matter does not mean that the subject matter has not been addressed by a federal statute. As such, the next section re-

72. See FDA CENTER FOR BIOLOGICS EVALUATION AND RESEARCH [CBER], POINTS TO CONSIDER IN THE MANUFACTURE AND TESTING OF THERAPEUTIC PRODUCTS FOR HUMAN USE DERIVED FROM TRANSGENIC ANIMALS (1995) [hereinafter CBER, POINTS TO CONSIDER]; U.S. DEPT. OF HEALTH AND HUMAN SERVICES & CBER, ANIMAL, PRODUCT, PRECLINICAL, AND CLINICAL ISSUES CONCERNING THE USE OF XENOTRANSPLANTATION PRODUCTS IN HUMANS (2003).

73. CBER, POINTS TO CONSIDER, *supra* note 72, at 2.

Biological products, including cellular therapies, are regulated by CBER under authority of the Public Health Service Act (42 U.S.C., Sec. 201 et seq.) and the Federal Food, Drug, and Cosmetic Act (21 U.S.C., Sec. 301 et seq.). The regulations are found at Title 21 of the Code of Federal Regulations (21 CFR). Therapeutic products for use in humans not regulated as biologics may be regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Devices and Radiological Health (CDRH). In addition, FDA's Center for Veterinary Medicine (CVM) and Center for Food Safety and Applied Nutrition (CFSAN) and the United States Department of Agriculture (USDA) have regulatory responsibility for veterinary and food safety issues associated with final products and the use of transgenic animals.

Id. at 2–3.

74. CBER, GUIDANCE FOR INDUSTRY: SOURCE ANIMAL, PRODUCT, PRECLINICAL, AND CLINICAL ISSUES CONCERNING THE USE OF XENOTRANSPLANTATION PRODUCTS IN HUMANS 7 (2003).

views the FDCA in order to determine whether the FDA's ignorance of the self-acting nature of the GE animals was reasonable.

C. *GE Mosquitoes Might Qualify as Extralabel Use*

If it is indeed the case that the GE mosquito is separable into two different products, the self-limiting gene and the living organism itself, then the GE mosquito should pass two sets of regulations, one for each product, or alternatively, just one regulation that addresses the safety and efficacy of both products.

The current requirements for a new animal drug application (NADA) are listed in Section 512(b)(1) of the FDCA⁷⁵ and more thoroughly explained in the FDA's regulations.⁷⁶ Although the FDA, in its Guidance for Industry document, asserts that the intended use of the resulting GE animal should be provided in the application,⁷⁷ no such language can actually be found in its regulation.⁷⁸ The Guidance for Industry document might have a non-binding effect on the NADA applicant, evidenced by the "Contains Non-Binding Recommendations" disclaimer clearly marked on the top of every page of the document.⁷⁹ Taken literally, no binding requirement exists for the GE animal producer to separately reveal the intended purpose of the GE animal itself. Moreover, neither the FDA regulation nor the guidance document provides requirements for labeling or safety and efficacy directed towards the GE animal itself; the requirements are only directed towards the "new animal drug," which is the self-limiting gene in the case of the GE mosquitoes.⁸⁰ In other words, only the labeling, safety, and efficacy requirements of the self-limiting gene have to be satisfied, and no such information has to be provided regarding the GE mosquito itself in order to get an approval for the GE mosquitoes.

If it is assumed that because of the lack of extra layer of regulation on the GE mosquitoes, Oxitec failed to describe on its label for the GE mosquitoes that the mosquitoes are intended to kill other mosquitoes or to miti-

75. 21 U.S.C. § 360b (2012).

76. 21 C.F.R. § 514.1 (2016).

77. FDA GUIDANCE, *supra* note 42, at 14.

78. 21 C.F.R. § 514.1(b).

79. If the guidance document is considered to be merely an interpretive rule, then the court might find that it is binding despite the lack of notice and comment rulemaking. *Perez v. Mortg. Bankers Ass'n*, 135 S. Ct. 1199, 1206 (2015). On the other hand, if a document characterized by an agency as a policy or guidance document in fact imposes new and substantive requirements on the regulated community, that document might require notice and comment rulemaking. *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1024 (D.C. Cir. 2000).

80. FDA GUIDANCE, *supra* note 42, at 14–20; 21 C.F.R. § 514.1(b).

gate humans' exposure to disease, then Oxitec is making promotional statements both on its website and through mass media that are beyond the scope of its label. For drugs intended for human therapeutic use, some of the largest settlements for civil and criminal allegations have involved issues of pharmaceutical companies marketing their drugs for uses other than the ones approved by the FDA.⁸¹ In animal drugs, a concept similar to the off-label use would be "extralabel use," a term which was introduced in the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994.⁸² Under the FDA regulations "extralabel use" is defined as:

[A]ctual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.⁸³

The language of the regulation suggests that only the use or intended use "in an animal" is considered as an extralabel use that is forbidden by the regulation. Killing other mosquitoes by breeding and giving birth to offspring could arguably be a use "in an animal" since the self-limiting gene is inherited "in" the offspring. Therefore, it could be argued that the self-limiting gene affecting the parent mosquito is an approved use of the new animal drug, but the mosquito itself affecting the offspring is an extralabel use.

Alternatively, it could be argued that the examples given in the second sentence of the definition only refer to drugs that are administrable by a veterinarian—animal drugs in a traditional sense. However, the rDNA constructs that are not animal drugs in a traditional sense are not explicitly mentioned in the regulation as examples of drugs. Many requirements delineated in the FDA's regulation only consider chemical compound drugs, as evidenced by NADA requirements that explicitly ask the applicant to provide information on the "chemistry"⁸⁴ and "components and composition" of chemicals.⁸⁵ Therefore, if the FDA decided to apply its regulations to rDNA, then the examples of possible extralabel uses explicitly mentioned

81. See, e.g., Gardiner Harris, *Pfizer Pays \$2.3 Billion to Settle Marketing Case*, N.Y. TIMES (Sept. 2, 2009), <http://www.nytimes.com/2009/09/03/business/03health.html>.

82. 21 USC § 360b(a)(4)–(5) (2012); 21 C.F.R. pt. 530 (2016).

83. 21 C.F.R. § 530.3(a).

84. 21 C.F.R. § 514.1(b)(2)(i).

85. 21 CFR § 514.1(b)(4).

in its regulation should not forbid the agency from applying the extralabel regulation to an animal itself as long as its definition is met.

However, even if Oxitec's promotional activities regarding the intended use of the GE mosquito itself qualify as extralabel use, the Second Circuit has recently decided that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug,"⁸⁶ which implies that Oxitec at least has a First Amendment defense if the mosquitoes are indeed effective at killing other mosquitoes.

Another potential problem stemming from the extralabel use of the GE mosquito is the AMDUCA's mention of "residue." The statute states that any extralabel use which results in residues that "present a risk to the public health" should not be permitted and that "[s]afe levels may be established . . . by regulation or order."⁸⁷ A definition of "residue" is not given in the FDCA. Instead, the word is used in the context of "pesticide chemical residue"⁸⁸ and food additives.⁸⁹

If there is no case of extralabel use, the FDA guidance only requires that a "NADA include method(s) and data to enable determination of residues of the new animal drug in food-producing animals, except when data or other adequate information establish that it is not reasonable to expect the new animal drug to become a component of food at concentrations considered unsafe."⁹⁰ Restricting the requirement for measurement of residue just to "food-producing animals" is not consistent with the purpose of the FDCA that requires all approved drugs to be safe to public health. Since the GE mosquitoes would not be used as food for humans, it is likely that the FDA will not require Oxitec to present data on how the rDNA residue can be measured and assessed, both in the environment and in other animals and humans, unless an accusation of extralabel use is made.

Mosquitoes are an important source of food for many animals in the environment, and even if humans do not directly consume mosquitoes, they could be exposed to the residue of the self-limiting gene.⁹¹ Therefore, not

86. United States v. Caronia, 703 F.3d 149, 169 (2d Cir. 2012).

87. 21 U.S.C. § 360b(a)(4)(B).

88. See 21 U.S.C. § 321(q)(2) (2012).

89. See 21 U.S.C. § 348(c)(3) (2012).

90. FDA GUIDANCE, *supra* note 42, at 18.

91. Generally, there is lack of proof on whether female modified mosquitoes are capable of spreading genetic material through bites or whether modified genetic materials would remain in the environment after the mosquitoes serve their purpose. As stated in Section I of this Note, the safety of GE mosquitoes is a scientific inquiry. This section of the Note is only addressing the gap in regulations that fail to require such scientific study assessing whether the technology is safe. See Helen Wallace, *Genetically Modified Mosquitoes Have Few Proven Benefits, Too Many Risks*, N.Y. TIMES (Feb. 23, 2015), <http://www.nytimes.com/room->

only should the issue of residue be within the scope of the National Environmental Policy Act (NEPA), which requires the FDA to review environmental risks of every NADA,⁹² the issue should also be within the purview of the FDCA.

The cause of those legislative drafting gaps might be that neither Congress nor the FDA was able to foresee the necessity of addressing the self-acting nature of GE animals. In other words, the residue problem would not have surfaced had the GE mosquitoes been kept in the lab, but once they go out into the wild as self-acting organisms and start interacting with the environment, problems not adequately addressed by the statute such as extralabel use and residue occur.

In summary, the GE mosquito project does not fit within the current FDCA because it is mischaracterized as an “animal drug.” That begs the question why other government agencies such as the U.S. Department of Agriculture (USDA) have failed to assert their authority on the jurisdiction of GE mosquitoes, despite their authoritative roles on the regulation of other GE animals. Therefore, it is necessary to explore the overall interaction of different government agencies in the subject matter of GE animals.

III. FDA SHOULD NOT BE THE ONLY AGENCY WITH JURISDICTION OVER GE MOSQUITOES

As discussed in Section II, the GE mosquito technology is mischaracterized under the FDA’s current jurisdiction. This poor fit begs the exploration of other existing options for regulating the GE mosquitoes. The USDA asserting jurisdiction over GE mosquitoes might have been more consistent with its past assertions of jurisdiction over GE insects. However, the USDA voluntarily abrogated its jurisdiction on GE mosquitoes, which is questionable given its extensive experience dealing with GE insects. The unclear assertion of jurisdiction by the FDA could give rise to a lawsuit like the one challenging the FDA’s authority to regulate the GE salmon.⁹³

fordebate/2015/02/23/can-genetically-modified-mosquitoes-eliminate-dengue-fever/genetically-modified-mosquitoes-have-few-proven-benefits-too-many-risks; Jennifer Kay, *Genetically Modified Mosquitoes No Danger to Humans or Environment, FDA Says*, WASH. POST (Mar. 12, 2016), https://www.washingtonpost.com/politics/genetically-modified-mosquitoes-no-danger-to-humans-or-environment-fda-says/2016/03/12/bd55dc52-e889-11e5-b0fd-073d5930a7b7_story.html?utm_term=.0ddb2ca49d2e.

92. FDA, *supra* note 48.

93. See, e.g., Complaint ¶ 11, *Institute for Fisheries Resources v. Burwell*, 2016 WL 4529517 (Aug. 30, 2016 N.D. Cal.) (No. 3:16-cv-01574), http://www.biologicaldiversity.org/campaigns/ge_seafood/pdfs/2016-3-30-dkt-1-pls-complaint_94703.pdf. In this case, the plaintiffs allege that the FDA lacked explicit “statutory authority to regulate GE animals as a

A. Coordinated Framework Is Not Intuitive

The Coordinated Framework for Regulation of Biotechnology was announced in 1986 and updated in 1992 by the Executive Office of the President, Office of Science and Technology Policy (OSTP) to outline the federal agencies' policies towards regulation of products derived from biotechnology including genetic engineering.⁹⁴ The policy states that “[e]xisting statutes provide a basic network of agency jurisdiction over both research and products; this network forms the basis of this coordinated framework and helps assure reasonable safeguards for the public.”⁹⁵ Rather than adding any new rationale to the logic of why GE animals have to be categorized into “animal drug,” the policy merely reiterates the regulatory jurisdictions asserted by three government agencies, the USDA, Environmental Protection Agency (EPA), and FDA. In other words, the policy stated that no new regulations are necessary for products derived from genetic engineering and that interpretation of the existing statutes is enough to accommodate the new technologies.

This is a reasonable policy considering the fact that it comes from the executive branch rather than from the judicial or legislative branches. However, the framework is outdated. Even the Executive Office of the President recognized the problem and issued a memorandum titled “Modernizing the Regulatory System for Biotechnology Products” on July 2, 2015.⁹⁶ The memorandum created a working group that was tasked with clarifying “the roles that each agency plays for different product areas, particularly for those product areas that fall within the responsibility of multiple agencies, and how those roles relate to each other in the course of a regulatory assessment.”⁹⁷

The result of this effort came 14 months later in the September 2016 proposed document titled “Modernizing the Regulatory System for Biotechnology Products: An Update to the Coordinated Framework for the

‘new animal drug’” and Congress did not intend for FDA to have authority to regulate GE animals because they require “different expertise, analyses, and regulation that were contemplated when Congress enacted the FFDCAs.” *Id.*

94. See generally Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23302, 23302 (Jun. 26 1986), http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf.

95. *Id.*

96. Executive Office of the President, *Memorandum for Head of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture: Modernizing the Regulatory System for Biotechnology Products* (July 2, 2015), https://www.epa.gov/sites/production/files/2016-12/documents/modernizing_the_reg_system_for_biotech_products_memo_final.pdf [hereinafter *Modernizing the Regulatory System for Biotechnology Products*].

97. *Id.* at 3.

Regulation of Biotechnology.”⁹⁸ However, the updated framework does nothing to change the way GE mosquitoes are regulated. It simply states that the “FDA regulates GE animals under the new animal drug provisions of the FD&C Act and FDA’s implementing regulations” without offering any new insight into why the FDA should have the sole authority over these animals.⁹⁹ Instead, it lauds the FDA’s Guidance for Industry document published in 2015 by stating that the guidance “clarifies FDA’s approach to regulating GE animals and provides recommendations to help producers of GE animals meet their responsibilities under the law.”¹⁰⁰

Perhaps the biggest problem with the framework is that it is not intuitive. Because one of the two main purposes of releasing GE mosquitoes is to reduce the population of mosquitoes,¹⁰¹ one might intuitively think that the USDA and the EPA should also have jurisdiction on the GE mosquitoes due to their agency expertise on insects and the environment, respectively. In fact, this was the intuition that the government agencies initially had when, in 2009, Oxitec started asking which federal agency it needed approval from regarding the GE mosquito project. The USDA initially claimed jurisdiction over the project, so in March 2010, Oxitec filed an application for importation of GE mosquitoes into the U.S. from the U.K.¹⁰² The USDA rescinded its jurisdiction over the GE mosquitoes after an 18-month delay.¹⁰³ It has been reported that the USDA avoided jurisdiction in October 2011 by determining that the project poses no threat to animal health.¹⁰⁴

The FDA asserts jurisdiction because the GE mosquitoes affect the structure and function of other mosquitoes in the wild; the USDA’s rationale for declining jurisdiction is that those effects do not amount to a threat to animal health. That rationale is not intuitive. Also, even if it is conceded that the other main purpose of the project—preventing human exposure to tropical disease—is why the FDA should have jurisdiction, the veterinary department of the FDA has jurisdiction, rather than the human health department.

98. Executive Office of the President, *Modernizing the Regulatory System for Biotechnology Products: An Update to the Coordinated Framework for the Regulation of Biotechnology* (proposed Sept. 2016), https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf.

99. *Id.* at 16.

100. *Id.* at 17.

101. Oxitec, *Overview*, *supra* note 6.

102. Joe Palca, *Biotech Firms Caught in Regulatory No Man’s Land*, NPR (Jan. 3, 2014 12:01 AM), <http://www.npr.org/2012/01/02/144330629/biotech-firms-caught-in-regulatory-no-mans-land>.

103. *Id.*

104. Friends of the Earth, *supra* note 49.

All of this confusion happened even after the FDA came out with the first version of the Guidance for Industry document in June 2015, which stated that the GE animals would be regulated under the FDCA as an “animal drug.”¹⁰⁵ This confusion indicates that the GE mosquito project fits awkwardly in the current Coordinated Framework and demonstrates just how farfetched the interpretation of the current statutes is to justify the FDA’s sole jurisdiction over the project.

The Coordinated Framework allows different government agencies to assert jurisdiction on the same project. For example, the FDA is the lead agency and the Food Safety and Inspection Service (FSIS), which is an agency in the USDA, is the supporting agency for the approval of foods and food additives made from genetic engineering.¹⁰⁶ Also, the EPA is the lead agency and the Animal and Plant Health Inspection Services (APHIS), which is also an agency in the USDA, is the supporting agency for the approval of pesticide microorganisms released in the environment.¹⁰⁷

Of course, there is no doubt that the FDA will consult with the USDA and EPA when making decisions regarding the approval of the GE mosquito project because of the NEPA requirements regarding premarketing approvals of FDA-regulated products.¹⁰⁸ However, it remains to be seen whether the counterintuitive policy of the Coordinated Framework allowing FDA to be the sole decision maker on the GE mosquito project has any bearing on the authority of the USDA and EPA on the project.

B. *FDA’s Assertion of Jurisdiction Might Be Inconsistent*

Even if the framework is counter-intuitive, judicial action is not likely to overturn the FDA’s assertion of jurisdiction over the GE mosquitoes because there is lack of any clear statutory act giving sole authority to any other particular government agency over the GE mosquito project. Also, the deference given by the judicial body to agency interpretation of statutes might make the FDA’s assertion of jurisdiction stronger in the face of a judicial challenge. The Supreme Court has specifically stated that legislation “such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act’s overriding purpose to protect the public health.”¹⁰⁹

105. See *supra* Section II.A. and accompanying notes.

106. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,304 (Jun. 26 1986), http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf.

107. *Id.*

108. 21 C.F.R. pt. 25 (2016).

109. *United States v. Article of Drug Bacto-Unidisk*, 394 U.S. 784, 798 (1969).

The remaining question is whether the FDA's past assertions of jurisdiction over GE animals have been consistent. The consistency of the FDA's assertion of jurisdiction was deemed important when the Eighth Circuit concluded that, although a literal reading of the definition of "drug" under the FDCA included animal biologics, the FDA lacked prior enforcement activity on them and therefore, animal biologics are not "drugs" under the FDCA.¹¹⁰

At first glance, the USDA seems to have been the major player in regulating GE animals. The USDA in 2008 released the world's first Environmental Impact Statement (EIS) on the GE fruit fly and pink bollworm in the APHIS plant pest control program.¹¹¹ This EIS has been widely used as the basis for regulatory approvals of other genetically engineered insects. For example, the USDA had sole jurisdiction over GE diamondback moths.¹¹² These moths were also developed and produced by Oxitec using the same concept of self-limiting genes.¹¹³ They have since been released as a part of an outdoor field trial in New York state.¹¹⁴ Meanwhile, the first and only approval of GE animals made by the FDA under the FDCA was for AquAdvantage Salmon, an "[a]tlantic salmon that reaches market size more quickly than non-GE farm-raised Atlantic salmon."¹¹⁵

These past GE animal projects do not provide conclusive evidence of whether the FDA's assertion of jurisdiction has been consistent. The GE fruit fly, pink bollworm, and diamondback moths are regarded as pests, while the AquAdvantage salmon is a food product. Unlike GE mosquitoes, production of salmon is not intended to affect the public health. However, one important point is that the self-limiting gene for the GE moth did not have to go through FDA approval.

110. See *Grand Laboratories, Inc. v. Harris*, 644 F.2d 729, 734–35 (1981).

111. See USDA, *USE OF GENETICALLY ENGINEERED FRUIT FLY AND PINK BOLLWORM IN APHIS PLANT PEST CONTROL PROGRAMS* (Oct. 2008), http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf.

112. USDA, *Withdrawal of an EA for Field Release of GE Diamondback Moths*, OUR FOCUS, https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/sa_environmental_documents/sa_environmental_assessments/diamondback-moth-permit-withdrawal (last modified Nov. 7, 2016).

113. Oxitec, *Diamondback Moth*, AGRICULTURE, <http://www.oxitec.com/agriculture/our-products/diamond-back-moth/> (last visited Dec. 22, 2016).

114. Christina Sarich, *Genetically Modified Moths Released in New York*, NATURAL SOCIETY (June 19, 2016), <http://naturalsociety.com/outrage-oxitecs-gm-moths-are-released-in-new-york>.

115. Press Release, FDA, *FDA Takes Several Actions Involving Genetically Engineered Plants and Animals for Food* (Nov. 19, 2016), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473249.htm>.

In the Environmental Assessment of the GE moth project released by the USDA in May 2014, the USDA tried to explain why the FDA did not partake in the assertion of jurisdiction over the project:

FDA uses what is termed a consultation process to ensure that human food and animal feed safety issues or other regulatory issues (e.g., labeling) are resolved prior to commercial distribution of bioengineered food. The permit applicant did not undergo this voluntary consultation because GE diamondback moth is not anticipated to yield food or feed.¹¹⁶

This contradicts FDA's position regarding the GE mosquito, which is also not anticipated to yield food or feed. However, it is not clear that a court would conclude that such inconsistency amounts to arbitrary and capricious agency action.

C. *The Lawsuit Over GE Salmon Suggests That Potential Challengers Might Face Hurdles in Proving Standing*

Not everyone was convinced that the GE salmon approved by the FDA was best suited for FDA jurisdiction. In March 2016, nearly a dozen environmental groups filed a complaint in the Northern District of California over the FDA's approval of the GE salmon.¹¹⁷ The plaintiffs first alleged that the FDA lacks statutory authority to regulate GE animals as a "new animal drug" under the FDCA; that challenge was discussed above in Section II.¹¹⁸

Next, the plaintiffs alleged that FDA did not fully consider or disclose the environmental and other risks of allowing this project and that the statute does not grant the FDA authority to assert jurisdiction over the GE salmon application.¹¹⁹ The complaint alleged that the environmental assessment (EA) and the finding of no significant impact (FONSI) failed to "discuss or adequately evaluate myriad scientific questions regarding the risk of significant and irreversible environmental, ecological, and intertwined socioeconomic harms related to the production, commercialization, and proliferation of AquaBounty's GE fish."¹²⁰ It further claimed that the FDA ignored the threats cited by expert scientists that include the possibility of GE salmon escaping from the facilities where they are manufactured or

116. USDA, PROPOSAL TO PERMIT THE FIELD RELEASE OF GENETICALLY ENGINEERED DIAMONDBACK MOTH IN NEW YORK 7 (2014).

117. Complaint, *supra* note 93, ¶ 1.

118. *Id.* ¶ 11.

119. *Id.* ¶ 7-9.

120. *Id.* ¶ 8.

grown and interbreeding with wild endangered salmon, resulting in competition with them for food and space, or passing infectious diseases.¹²¹ That potential threat exists because of the “self-acting” nature of the GE salmon like that of the GE mosquito discussed in Section II.B. above.¹²² Such inadequate studies by the FDA, the complaint claims, “are the result of FDA’s failure to take the legally required ‘hard look’” and are thus arbitrary, capricious, and contrary to APA, National Environmental Policy Act (NEPA), ESA, and FDA Amendments Act.¹²³

Finally, the complaint added that “even if FDA had the authority to issue the GE Animal Guidance, the guidance itself fails to explain how FDA will substantively incorporate important environmental considerations into its assessment of safety and effectiveness as a part of the review and approval of GE animals.”¹²⁴ In other words, FDA failed to incorporate environmental risks as a part of its statutory “safety” evaluation.

The GE salmon complaint does not allege that the product is unsafe for human consumption—it only focuses on the potential environmental risks that might arise if the GE salmon interact with the natural population.¹²⁵ Natural mosquitoes, on the other hand, are less likely to be seen as subjects worth much protection. Unlike the natural population of salmon, mosquitoes are mostly seen as annoyances and disease-transmitters. Moreover, the scientific community thinks that the eradication of mosquitoes would not have any serious consequences for the ecosystem.¹²⁶

Here, proving standing would be the biggest hurdle for the potential challengers of the GE mosquito project.¹²⁷ Proving injury in fact for the GE salmon challengers might be easier because bigger GE salmon have survival advantages over the natural population.¹²⁸ With the scientific community approving the eradication of the mosquito population, the challengers of the GE mosquito project might have a more difficult time asserting that the GE mosquito project is a threat to the environment. Also, Oxitec

121. *Id.*

122. *See supra* Section II.A. and accompanying notes.

123. Complaint ¶ 9, *Institute for Fisheries Resources v. Burwell*, 2016 WL 4529517 (Aug. 30, 2016 N.D. Cal.) (No. 3:16-cv-01574).

124. *Id.* ¶ 12.

125. *See id.*

126. Janet Fang, *A World Without Mosquitos*, 466 *NATURE* 432, 434 (2010).

127. Standing requires the plaintiff to show an injury in fact, causation and redressability. *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560–61 (1992). Also, the GE salmon lawsuit was dismissed in August 2016 without the court addressing the question of standing. Therefore, the question of standing in the case is only speculative at this point.

128. *See e.g.*, Fredrik Sundström & Robert H. Devlin, *Increased Intrinsic Growth Rate is Advantageous Even Under Ecologically Stressful Conditions in Coho Salmon*, 25 *EVOLUTIONARY ECOLOGY* 447 (2011).

seems confident that the GE mosquito is not a threat to human health.¹²⁹ Without any substantive evidence pointing otherwise, proving injury in fact as an element of demonstrating standing might be difficult.

IV. REGULATORY LESSONS CAN BE LEARNED FROM ABROAD

Some residents of Key West might be relieved to know that a few other countries have already released Oxitec's GE mosquitoes without any report of negative effects.¹³⁰ In 2009 and 2010, 3.3 million mosquitoes were released in the Cayman Islands; 3 million in northeastern Brazil in 2011; and 6,000 in Malaysia in 2010.¹³¹ The troublesome part of these releases is that no international regulation specific to the release of GE mosquitoes has been developed.¹³² However, some countries, such as Mexico, have developed regulatory bodies tailored specifically for GE insects, including Oxitec's mosquitoes.¹³³

A. International Regulation Introduces the "Self-Acting" Concept

The World Health Organization (WHO) has published a guidance document for testing GE mosquitoes, but the document merely describes the current regulatory framework and gives vague recommendations of what the regulatory framework should encompass without any enforcement effect.¹³⁴ The guidance recognizes that "[e]ach country has its own sovereign regulatory process, but overarching international agreements or treaties also may be relevant" without much detail.¹³⁵

The Cartagena Protocol on Biosafety to the Convention on Biological Diversity is the closest thing the international community can rely on in judging whether the release of the mosquitoes would comply with international regulatory standards.¹³⁶ However, the protocol was mostly designed to oversee international trade of genetically modified agricultural products,

129. Oxitec, *Safety & Sustainability*, OUR SOLUTION, <http://www.oxitec.com/our-solution/safety-sustainability/> (last visited Dec. 22, 2016).

130. See Lim Li Ching, *GM Mosquitoes: Flying Through the Regulatory Gaps*, GENEWATCH, <http://www.councilforresponsiblegenetics.org/genewatch/GeneWatchPage.aspx?pageId=421> (last visited Dec. 5, 2016).

131. *Id.*

132. *See id.*

133. *See infra* Section IV.B.

134. WHO, GUIDANCE FRAMEWORK FOR TESTING OF GENETICALLY MODIFIED MOSQUITOES (2014), http://apps.who.int/iris/bitstream/10665/127889/1/9789241507486_eng.pdf?ua=1.

135. *Id.* at xxv.

136. See Graciela R. Oстера & Lawrence O. Gostin, *Biosafety Concerns Involving Genetically Modified Mosquitoes to Combat Malaria and Dengue in Developing Countries*, 305 JAMA 930, 931 (2011).

so its application to GE mosquitoes was questioned from the beginning.¹³⁷ In an attempt to resolve this problem, the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management to the Conference of the Parties attempted to provide specific guidelines for GE mosquitoes in Nagoya, Japan, in October 2010.¹³⁸ However, the group faced criticism that they did not address significant technical issues.¹³⁹ The U.S. is not a party to the Cartagena Protocol, which makes it unenforceable in the United States.¹⁴⁰

However, an important aspect of the WHO's guidance is its indirect recognition of the "self-acting" nature of the GE mosquito technology discussed in Section II.B. The WHO does not recognize the self-acting characteristics directly, but does indirectly by articulating the concept of a "self-sustaining" organism.¹⁴¹ "Self-sustaining" is defined by the WHO as an approach "where the heritable modification is spread and maintained indefinitely through the target population."¹⁴² Even though sterile insect techniques such as Oxitec's technology are categorized as self-limiting instead of self-sustaining by the WHO,¹⁴³ the mosquitoes released into the wild have at least transient self-sustaining characteristics until sufficient time passes for the elimination of the population through breeding and production of offspring. Because of this transient self-sustaining characteristic, concerns arise as to the movement of these mosquitoes, particularly regarding their transboundary movements.¹⁴⁴ In other words, international regulatory efforts to address the transboundary movements of the mosquitoes after their release into the wild are important in some cases because humans cannot control the spread or migration of GE mosquitoes after release.

Even though the release of mosquitoes in Key West might not require an international effort because the region is separated from any other country by a body of water, roads and boats still connect the region to the mainland U.S. The discussion of self-acting characteristics of the mosquitoes is still relevant domestically. Additionally, although the self-acting concept was only indirectly inferred from the WHO guidelines and did not play an important role in the discussions for international regulations, the concept

137. *See id.*

138. *Id.*

139. *Id.*

140. *List of Parties: Cartagena Protocol, CONVENTION ON BIOLOGICAL DIVERSITY*, <https://www.cbd.int/information/parties.shtml#tab=1> (last visited Dec. 22, 2016).

141. WHO, GUIDANCE FRAMEWORK FOR TESTING OF GENETICALLY MODIFIED MOSQUITOES, *supra* note 134, at 4 (discussing "self-sustaining" as a category recognizing a GE mosquitoes ability to persist following release).

142. *Id.* at xi.

143. *See id.* at 3–5.

144. *See id.* at xxv.

could still play an important role in setting the foundations for domestic regulations regarding the GE mosquitoes.

*B. Establishing a New Federal Regulatory Body:
Lessons From Mexico*

Mexico also confronted a lack of preexisting structure for regulating GE mosquitoes when it reviewed and approved a large outdoor field-cage study with Oxitec's OX3604C strain mosquitoes in a rural area near Tapachula, Mexico.¹⁴⁵ That strain is not the same as the OX513A that may be released in Florida, and no mosquitoes were actually released into the wild during the trial.¹⁴⁶ Nonetheless, it is worthwhile to observe how the regulatory system in Mexico treated this situation in order to see whether any lessons can be learned and applied in the U.S. context.

The authors of the field study in Mexico stated that the keys to the successful completion of the field experiment were engagement with the community as well as Mexico's "mature regulatory system for the use of genetically modified organisms."¹⁴⁷ One analysis of the field study points to three factors that were most important in allowing this contained field trial in Mexico.¹⁴⁸ The first factor was the existence of a federal-level regulatory body CIBIOGEM (Comisión Intersecretarial de Bioseguridad de los Organismos Genéticamente Modificados).¹⁴⁹ The second was the collaborative efforts of world-class scientific institutions.¹⁵⁰ The third was the efficient decision-making processes of local communities.¹⁵¹

The second and third factors are also present in the U.S. regulatory response. The Mexican response differs from the U.S. based on their regulatory approach to the use of GE animals. The U.S. government should not have any trouble finding the world's top experts in the field, and local organizations such as the Florida Keys Mosquito Control District facilitate discussions between Oxitec and the local residents.

The first factor is where Mexico differentiates itself in the efficient regulation of GE animals. CIBIOGEM is a federal-level commission that comprises the heads of the Ministries of Health, Agriculture, Livestock, Rural Development, Fisheries and Food (SAGARPA), Environment and

145. See Facchinelli et al., *Field Cage Studies and Progressive Evaluation of Genetically-Engineered Mosquitoes*, 7 PLOS NEGLECTED TROPICAL DISEASES 1, 1–2 (2013).

146. *Id.* at 2.

147. *Id.*

148. See Ramsey et al., *A Regulatory Structure for Working with Genetically Modified Mosquitoes: Lessons from Mexico*, 8 PLOS NEGLECTED TROPICAL DISEASES 1, 8 (2014).

149. *Id.*

150. *Id.*

151. *Id.*

Natural Resources (SEMARNAT), Finance and Public Credit, Economy and Public Education, and the General Director of the National Council of Science and Technology (CONACYT).¹⁵² CIBIOGEM legislation adopted in 2008 to regulate “the activities of contained and confined use, experimental release, release in a pilot program, commercial release, trading, importation, and exportation of GMOs” implements the Law on Biosafety of Genetically Modified Organisms.¹⁵³

The Executive Office of the President in the United States also established the Biotechnology Working Group under the Emerging Technologies Interagency Policy Coordination Committee in 2015.¹⁵⁴ This working group includes representatives from the Executive Office of the President, the EPA, FDA, and USDA.¹⁵⁵ However, one key difference between this working group and CIBIOGEM is that the purpose of the working group is merely coordination between different government agencies while that of CIBIOGEM includes the execution of legislation.¹⁵⁶

Rather than leading the effort to legislate and implement new laws, the Biotechnology Working Group in the U.S. merely asks the EPA, FDA, and USDA to commission independent studies by external institutions such as the National Academy of Sciences.¹⁵⁷ A legislative effort designed to specifically address the issues relating to GE animals might be a better way of dealing with new GE technologies rather than the method of trying to fit the new technologies into an outdated regulatory scheme adopted by the Coordinated Framework.

V. NEW REGULATORY SCHEMES SHOULD BE DEvised SOON

As Oxitec’s Florida Keys Project is nearing its implementation, various civil protests have arisen in response to anxiety among various interest groups that Oxitec’s application will be approved. An online petition opposing the application’s approval has been signed by more than 150,000 people.¹⁵⁸ A lawsuit has even been filed against the FDA for approving the

152. Francisco A. Laguna & Annapurna Nandyal, *Genetically Modified Organisms in Mexico*, TRANSLEGAL (Aug. 20, 2013), <https://translegallic.wordpress.com/2013/08/20/genetically-modified-organisms-in-mexico/comment-page-1>.

153. Ramsey et al., *supra* note 148, at 4.

154. *Modernizing the Regulatory System for Biotechnology Products*, *supra* note 96, at 3.

155. *Id.*

156. *See id.* at 3–4; Ramsey et al., *supra* note 148, at 4.

157. EXECUTIVE OFFICE OF THE PRESIDENT, NATIONAL STRATEGY FOR MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS 14 (2016), https://www.epa.gov/sites/production/files/2016-12/documents/biotech_national_strategy_final.pdf

158. *GE Mosquito Petition*, *supra* note 30.

project.¹⁵⁹ While it remains to be seen whether such congregation of interest groups could impose enough political pressure on the FDA, Oxitec has made significant progress in preparing for the approval.¹⁶⁰ Oxitec has already set up a lab in Marathon, Florida, for the purpose of importing mosquito eggs for injection of the self-limiting genes and the subsequent rearing of adult mosquitoes for release.¹⁶¹

At the same time, new ambitious projects employing genetic engineering technologies are springing up to tackle similar problems in other regions of the world, such as China.¹⁶² Also, the recent outbreak of the Zika virus in a section of Miami Beach has raised significant alarm in the U.S.¹⁶³

Human-driven science will consistently evolve to solve the world's most serious health problems. New versions of Oxitec's technology are being researched by many labs around the world. For example, MIT has announced that its scientists are developing a technology called "gene drive" to wipe out the population of mosquitoes that carry the Zika virus.¹⁶⁴

In order to effectively facilitate such innovative technologies, Congress should devise a new regulatory scheme that makes more intuitive sense rather than merely relying on outdated statutory language. The law is lagging behind the science, and the regulatory shortcoming fails to foster the public's confidence in the legislative process. Bridging the gap between science and law is especially important as we enter into an increasingly technical time with emerging innovations such as autonomous vehicles, sophisticated surveillance, and GM foods. It is extremely important that Congress take the responsibility for maintaining public faith in these complex fields in order to maintain their status as the creators of our federal law.

159. David Goodhue, *Environmental Groups to Sue FDA Over Plan to Release Zika-Fighting GMO Mosquitoes*, GENETIC LITERACY PROJECT (Nov. 29, 2016), <https://www.geneticliteracyproject.org/2016/11/29/environmental-groups-sue-fda-plan-release-zika-fighting-gmo-mosquitoes>.

160. Alvarez, *supra* note 25.

161. *Id.*

162. Cat DiStasio, *World's Largest 'Mosquito Factory' in China to Release 20 Million Bugs a Week*, INHABITAT (Mar. 30, 2016), <http://inhabitat.com/worlds-largest-mosquito-factory-in-china-to-release-20-million-bugs-a-week>.

163. E.g., Tiffany Ap, *Zika Virus: Miami Beach Transmission Zone Triples*, CNN (Sept. 17, 2016 2:55 AM), <http://www.cnn.com/2016/09/17/health/miami-beach-zika-zone-expanded/>.

164. Antonio Regalado, *We Have the Technology to Destroy All Zika Mosquitoes*, MIT TECHNOLOGY REVIEW (Feb. 8, 2016), <https://www.technologyreview.com/s/600689/we-have-the-technology-to-destroy-all-zika-mosquitoes>.