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ARTICLE

THE RISE OF THE MUTANTS: OBTAINING REGULATORY
APPROVAL FOR THE RELEASE OF GENETICALLY
MODIFIED MOSQUITOES[†]

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Over the last few decades, sterile insect technique has emerged as an attractive means of controlling insect populations. Recently, scientists have considered releasing genetically modified mosquitoes into the Florida Keys as a means of controlling the spread of certain exotic, insect-borne viruses. Although transgenic insects have previously been tested in the field, these organisms have traditionally been regulated under the authority of APHIS. The present technology, however, is pending approval as a “new animal drug” under the FDA. This Article seeks to shed light on this inconsistency by examining the legal framework surrounding the regulation of transgenic insects and discussing other instructive examples of transgenic animal regulation. Additionally, this Article examines the definition of “new animal drug” under the FDA and analyzes how the genetically modified mosquitoes might fall under that designation more appropriately than a product designation under the EPA or APHIS. This Article concludes by addressing some of the issues with the

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current biotech regulatory environment and proposing improvements to add clarity to a given transgenic insect's product designation.

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I. INTRODUCTION

As concerns over the emergence of new infectious diseases continue to grow, scientists are turning towards increasingly novel means of controlling disease spread. One such technique involves the release of genetically modified mosquitoes into the environment, which may curb the spread of certain insect-borne pathogens, such as dengue virus and chikungunya virus.¹ This technique is called the sterile insect technique (SIT), and it involves the introduction of genetically manipulated laboratory insects into the environment to bring about a reduction in the wild insect reservoir for these pathogens. SIT is an attractive alternative to traditional methods of insect control (namely, chemical insecticides); the use of which is increasingly limited by resistance among pests, risks of environmental contamination, and effects on non-target organisms.² Furthermore, the lack of specific drugs or vaccines against these viral diseases provides additional motivation for the employment of SIT technology.³ Despite considerable progress within the field, however, the widespread use of SIT continues to face obstacles in the form of both public opinion and regulatory challenges.⁴

The Coordinated Framework for the Regulation of Biotechnology, as promulgated by the Reagan Administration's Office of Science and Technology Policy, provides a jurisdictional map for the regulation of biotechnology products by various government agencies.⁵ Some transgenic insects have previously been tested in the field, and these organisms have traditionally been regulated as a biotechnology product under the authority of the Animal and Plant Health Inspection Service (APHIS).⁶ In contrast, the aforementioned mosquito technology is presently

1. Greg Allen, *Florida Health Officials Hope to Test GMO Mosquitoes This Spring*, NPR (Jan. 28, 2015, 5:28 PM), <http://www.npr.org/blogs/health/2015/01/28/382168407/florida-health-officials-hope-to-test-gmo-mosquitoes-this-spring>.

2. Camilla J. Beech et al., *Genetically Modified Insects: Science, Use, Status and Regulation*, 6 COLLECTION BIOSAFETY REV. 66, 68 (2012).

3. Luke Alphey & Nina Alphey, *Five Things to Know about Genetically Modified (GM) Insects for Vector Control*, PLOS PATHOG.10(3) e1003909, Mar. 2014, at 1.

4. *Id.* at 2.

5. VICTORIA SUTTON, LAW AND BIOTECHNOLOGY: CASES AND MATERIALS 36-41 (2007) (citing 51 Fed. Reg. 23,304).

6. See K.E. Hokanson et al., *Not All GMOs are Crop Plants: Non-Plant GMO Applications in Agriculture*, 23 TRANSGENIC RES. 1057, 1059 (2014).

pending approval as a “new animal drug” under the FDA.⁷ The FDA broadly defines a new animal drug as “any drug intended for use in animals other than man . . . [that] is not generally recognized as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling of the drug.”⁸ This seemingly inconsistent regulation of genetically modified insects creates confusion among parties interested in the expansion of these technologies (as well as parties interested in the regulation of biotechnology in general) and calls to question the efficacy of the current regulatory regime.

This Article will examine the regulatory environment surrounding genetically modified insects and discuss why genetically modified mosquitoes are more appropriately designated a “new animal drug” under FDA regulations rather than designated a “product” under EPA regulations or APHIS.⁹ In doing so, this Article will discuss the underlying legal framework corresponding to the regulation of biotechnology products and will consider the regulation of other transgenic insects, as well as some higher animals, by the FDA and other government agencies. This Article will then discuss the FDA’s definition of a new animal drug and will seek to identify the characteristics of an insect that result in regulation under the FDA. Finally, this Article will suggest improvements to the regulatory framework to add clarity to a genetically modified insect’s designation.

II. OXITEC’S GENETICALLY MODIFIED MOSQUITOES

Oxitec, a British biotech company, has developed genetically modified mosquitoes that harbor a lethal gene in their germ cells and are incapable of producing viable offspring.¹⁰ In order to accomplish this, Oxitec uses a DNA microinjection technique to introduce small amounts of modified DNA containing the lethal

7. Andrea Gerlin, *Mosquitoes Shoot Blanks in Scientist’s Air War on Dengue*, BLOOMBERG (May 4, 2012, 7:01 PM), <http://www.bloomberg.com/news/articles/2012-05-03/mosquitoes-shoot-blanks-in-scientist-s-air-war-on-dengue>.

8. *New Animal Drug Applications*, FDA, <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/NewAnimalDrugApplications/> (last updated Jan. 7, 2015) (citing 21 U.S.C. § 321(v)).

9. 21 U.S.C. § 321(v) (2009).

10. *More on the Science: How Does Oxitec Make Genetically Modified Mosquitoes?*, OXITEC, <http://www.oxitec.com/oxitec-video/more-on-the-science-how-does-oxitec-make-genetically-modified-mosquitoes/> (last visited May 1, 2015).

gene directly into mosquito eggs.¹¹ Some of this DNA will be naturally incorporated into the genome of the developing mosquitoes; this process occasionally occurs in the sperm cells of developing male mosquitoes and the egg cells of developing female mosquitoes.¹² The newly incorporated DNA (and the lethal gene) can then be passed on to the developing mosquitoes' future offspring, which require the presence of a specific antibiotic (tetracycline) in order to survive to adulthood.¹³ When released, the genetically modified mosquitoes compete with wild mosquitoes for mates. But unlike wild mosquitoes, these transgenic mosquitoes produce only non-viable offspring in the absence of tetracycline. Eventually, this leads to an overall reduction in the mosquito population.¹⁴

With these genetically modified mosquitoes, Oxitec hopes to curb the natural population of a particular mosquito species, *Aedes aegypti*, which serves as the natural insect reservoir for dengue virus and chikungunya virus.¹⁵ Dengue virus emerged as a worldwide problem in the 1950s and is currently a leading cause of illness and death in the tropics and subtropics.¹⁶ Dengue presents as a high fever in combination with at least two other disease manifestations, including severe headache, severe eye pain, joint pain, muscle and/or bone pain, rash, mild bleeding, and low white cell count.¹⁷ An exacerbated disease state may arise in the form of dengue hemorrhagic fever, which can ultimately result in failure of the circulatory system, shock, and possibly death.¹⁸ Chikungunya is a similar acute febrile illness that may result in debilitating bilateral polyarthralgia and in some cases, arthritis.¹⁹

In order to evaluate the potential of the genetically modified mosquitoes to reduce the population of *A. aegypti* in the environment, Oxitec (in conjunction with the Florida Keys

11. *Id.*

12. *Id.*

13. *Id.*

14. *Id.*

15. See *Florida Keys Project*, OXITEC, <http://www.oxitec.com/health/florida-keys-project/> (last visited May 1, 2015).

16. *Dengue*, CDC, <http://www.cdc.gov/Dengue/> (last updated Mar. 26, 2015).

17. *Symptoms and What To Do if You Think You Have Dengue*, CDC, <http://www.cdc.gov/dengue/Symptoms/index.html> (last updated Sept. 27, 2012).

18. *Id.*

19. Tyler M. Sharp, *Differentiating Chikungunya From Dengue: A Clinical Challenge*, MEDSCAPE (Sept. 15, 2014), <http://www.medscape.com/viewarticle/831523>.

Mosquito Control District) has proposed to release the genetically modified mosquitoes into the Florida Keys for a field trial.²⁰ Similar field trials have already been conducted in the Cayman Islands, Malaysia, Panama, and Brazil, and in each case have demonstrated a reduction of the local *A. aegypti* population by over 90%.²¹ The proposed field trial would involve the release of genetically modified male mosquitoes, which are incapable of biting humans and thus do not spread disease.²² The goal is for the released sterile males to compete with wild male mosquitoes for mates, which would successively reduce the viability of future mosquito generations.²³ Current estimates indicate that a release of over 40,000 sterile male mosquitoes could ultimately result in the complete eradication of *A. aegypti* in a localized environment.²⁴ Because *A. aegypti* is a non-native species in the United States, some have viewed the removal of this insect vector from the Florida Keys as benefit to the environment.²⁵

III. THE REGULATION OF BIOTECHNOLOGY

A. Coordinated Framework for the Regulation of Biotechnology

The Coordinated Framework for the Regulation of Biotechnology (The Framework) details the responsibilities of various governmental agencies in the regulation of various aspects of biotechnology.²⁶ This Framework was formed in response to mounting scientific and governmental concerns regarding the risk of genetic engineering experiments progressing during the 1970s and 1980s.²⁷ Specifically, the Framework uses existing statutes to “[P]rovide a network of agency control over biotechnology’s research and products sufficient for the regulation of the plants, animals, and microorganisms created by the new genetic

20. Florida Keys Project, *supra* note 15; see also *Our History*, FLA. KEYS MOSQUITO CONTROL DISTRICT, <http://keysmosquito.org/history/> (last visited Apr. 6, 2016) (explaining the purpose of the Florida Keys Mosquito Control District to improve quality of life of residents by employing effective measures to control the spread of mosquito-borne diseases).

21. Florida Keys Project, *supra* note 15.

22. *Id.*

23. *Id.*

24. Regina Jijoho Patinvoh & Alfred Akpoveta Susu, *Mathematical Modelling of Sterile Insect Technology for Mosquito Control*, 2 ADVANCES ENTOMOLOGY 180, 189 (2014).

25. Allen, *supra* note 1.

26. Sutton, *supra* note 5.

27. See *id.* at 34–36.

engineering techniques.”²⁸ The major regulatory agencies addressed in the Framework include the FDA, EPA, and APHIS.²⁹ Charts 1 and 2 of the Framework provide lists of the commercial biotechnology products and research areas that are subject to approval by each of these agencies.³⁰ For each of these products, however, it is important to consider that jurisdiction is premised on use of the product and may shift according to the product’s specific proposed use.³¹

The FDA’s biotechnology jurisdiction extends to foods, food additives, human drugs, medical devices, biologics, and animal drugs.³² If, however, a food product is prepared from domestic livestock or poultry, jurisdiction will shift to the Food Safety and Inspection Service (FSIS).³³ In addition to these delineated categories, FDA may also become involved in a product’s regulation if its use involves the implementation of pesticide tolerances for foods.³⁴

EPA’s biotechnology jurisdiction includes certain closed-system uses of intergeneric microorganisms, microbial pesticides, and certain situations involving release of microorganisms into the environment.³⁵ If a microbial pesticide is also a plant pest, animal pathogen, or regulated article requiring a permit for shipment or release, APHIS will also become involved in the regulatory process.³⁶ Additionally, for uses involving the release of microorganisms into the environment, jurisdiction will depend on the characteristics of the organism as well as its specific use.³⁷

APHIS regulates biotechnology activities that involve animal biologics, plants, seeds, plant pests, animal pathogens, and “regulated articles.”³⁸ These articles encompass certain genetically engineered organisms containing genetic material from plant pests.³⁹ If the contemplated use involves the shipment or release of

28. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302–23,303 (June 26, 1986).

29. *Id.* at 23,304.

30. *Id.* at Chart 1 & Chart 2.

31. *Id.*

32. *Id.*

33. *Id.*

34. *Id.*

35. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,304 at Chart 1 & Chart 2 (June 26, 1986).

36. *Id.*

37. *Id.*

38. *Id.*

39. *Id.*

such regulated articles into the environment, or the shipment of a plant pest or animal pathogen, a permit issued by APHIS will be required.⁴⁰ In addition, APHIS is responsible for the regulation of certain intrageneric pathogenic organisms and non-engineered pathogenic organisms, but only if the use of those organisms is tied to agriculture.⁴¹ For situations involving the release of intrageneric pathogenic organisms developed via commercial funding, EPA serves as the lead regulatory authority.⁴²

Issues may arise with respect to life forms that do not neatly fit into one the above circumscribed categories, as well as biotechnology work that does not have an end product.⁴³ If the experimental release of genetically modified organisms does not involve a commercial product, does not involve the work of scientists receiving government funding, and does not come under an experimental use permit section of the law, the Framework does not apply.⁴⁴ Additionally, the Framework was limited in its application to two classes of organisms—those containing genetic material from different genera and microorganisms containing genetic material from pathogens.⁴⁵ In order to address this issue, the Office of Science and Technology Policy of the President (OSTP) eventually broadened the application of the Framework to all “organisms with deliberately modified hereditary traits.”⁴⁶ But the OSTP also reduced the overall regulatory burden on the scientific community by narrowing the regulatory oversight to situations in which the risk posed by introduction of the organism is established by existing information.⁴⁷ These changes ensure that certain modified organisms do not escape regulation, while ensuring that oversight is grounded in existing information.

B. Application of NEPA to Genetically Modified Organisms

Any agency contemplating the regulation of a genetically modified organism will need to consider the implications of the National Environmental Policy Act (NEPA) if field tests with the organism are involved. NEPA was enacted in 1970 in an effort to

40. *Id.*

41. *Id.*

42. *Id.*

43. SUTTON, *supra* note 5, at 40.

44. *Id.*

45. *Id.*

46. Planned Introduction Into Environment of Organisms With Modified Hereditary Traits, 55 Fed. Reg. 31,120 (1990).

47. *Id.*

establish national policies and goals aimed at promoting the enhancement of the environment.⁴⁸ NEPA requires federal agencies “[to] include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement . . . on the environmental impact of the proposed action.”⁴⁹ A “major federal action” includes “actions with effects that may be major and which are potentially subject to Federal control and responsibility.”⁵⁰ Such actions tend to fall within one of four categories: (1) adoption of official policy; (2) adoption of formal plans; (3) adoption of programs; and (4) approval of specific projects.⁵¹

If an agency is engaging in a major federal action, the agency must either prepare an “environmental impact statement (EIS)” examining the environmental impact of the proposed action,⁵² prepare an “environmental assessment (EA)” assessing whether or not to prepare an EIS,⁵³ or determine that the action falls within a categorical exclusion.⁵⁴ If an agency’s action does not fall within a categorical exclusion, the preparation of an EA prior to an EIS may prove beneficial, as an EA is described as a concise document that serves to “(1) briefly provide sufficient evidence and analysis for determining whether to prepare an [EIS] or a ‘finding of no significant impact (FONSI)’; (2) aid an agency’s compliance with [NEPA] when no [EIS] is necessary; and (3) facilitate preparation of [an EIS] when one is necessary.”⁵⁵ If the EA yields a finding of no significant impact with respect to the action’s effect on the human environment, no EIS need be prepared.⁵⁶

At present, the proposed mosquito field tests in Florida are on hold pending the FDA’s approval of the Oxitec technology as a “new animal drug.”⁵⁷ If the FDA determines that the field tests can proceed, this decision would seem to fall squarely within the “approval of specific projects” arm of a major federal action under NEPA. The FDA will therefore likely be required to prepare an EA assessing the field tests. The proposed field tests will likely be

48. National Environmental Protection Act, 42 U.S.C. § 4321 (1970).

49. *Id.* at § 4332(2) (c)(I).

50. 40 C.F.R. § 1508.18 (1978).

51. *Id.* at § 1508.18(b)(1–4).

52. *Id.* at § 1508.11.

53. *Id.* at § 1508.9.

54. *Id.* at § 1508.4.

55. *Id.* at § 1508.9.

56. *Id.* at § 1508.13.

57. Florida Keys Project, *supra* note 15.

found to have a significant impact on the human environment because the anticipated reduction in the mosquito population and associated reduction in the spread of viral infectious diseases will have a direct effect on human health via environmental modulation. Accordingly, the FDA will likely be required to prepare an EIS in compliance with the strictures of NEPA.

IV. THE REGULATION OF OTHER GENETICALLY MODIFIED ORGANISMS

A. *Previous Regulation of Genetically Modified Arthropods under APHIS*

Aside from a bare analysis of the Framework and applicable statutes, additional insight into the categorization of the Oxitec mosquitoes can be gleaned by examining the regulation of other genetically modified arthropods. Two such organisms have previously come under federal regulatory control—the western orchard predatory mite and the pink bollworm. APHIS served as the primary regulatory agency for field testing of both organisms, and EAs were prepared in accordance with NEPA. The transgenic pink bollworms were considered to fall under the jurisdiction of APHIS because the organism is a plant pest, rendering it subject to regulation under 7 C.F.R. § 340.⁵⁸

1. Western Orchard Predatory Mite

The western orchard predatory mite, *Metaseiulus occidentalis*, is a beneficial organism that preys on phytophagous spider mites, such as the two-spotted spider mite, *Tetranychus urticae*.⁵⁹ The two-spotted spider mite is a “pest in deciduous orchards of apples, almonds, walnuts, pears, and peaches, as well as in vineyards and strawberry and hop plantations.”⁶⁰ As a predator of the two-spotted spider mite, the western orchard predatory mite thus improves the health of orchards and plantations by removing these pests from the environment. Beginning in the spring of 1996, transgenic predatory mites containing the bacteria *Escherichia coli* gene *lacZ* were released into Alachua County, Florida.⁶¹ The *lacZ* gene produces the enzyme β -galactosidase, which stains the tissue of the

58. *Id.*

59. GENETICALLY ENGINEERED ORGANISMS: ASSESSING ENVIRONMENTAL AND HUMAN HEALTH EFFECTS 263 (Deborah K. Letourneau & Beth Elpern Burrows eds., 2002) [hereinafter ORGANISMS].

60. *Id.*

61. *Id.*

organism dark blue in the presence of certain chemicals.⁶² Unfortunately, the released mites quickly faced environmental challenges in the form of heavy rains and freezing temperatures (with a concomitant decline in host plant quality), which ultimately resulted in the crash of the transgenic population.⁶³ Six more colonies were released later in the year, but the transgene was rapidly lost from all of the released colonies.⁶⁴

Before this field test, a single environmental release permit for the field tests with transgenic *M. occidentalis* was issued by APHIS.⁶⁵ Regulatory approval of the field tests was granted after the preparation of an EA, resulting in a subsequent FONSI.⁶⁶ In the EA and FONSI, APHIS considered data submitted by the researchers and conducted a review of other relevant literature to determine that the organism would “not present a risk of plant pest introduction or dissemination and [would] not have a significant impact on the quality of the human environment.”⁶⁷ Because the release of the predatory mites in the field test was determined to have no significant impact on the environment, no EIS was prepared.⁶⁸

2. Pink Bollworm

The pink bollworm, *Pectinophora gossypiella*, is a highly destructive pest of cotton, costing American cotton producers in excess of \$32 million each year due to control efforts and yield losses.⁶⁹ The USDA began efforts to eradicate the pink bollworm in 2001 as part of a multi-phase approach advocated by the National Cotton Council.⁷⁰ The approach stretches across four

62. James K. Presnail & Marjorie A. Hoy, *Transient expression of a Drosophila melanogaster hsp70 promoter/lacZ construct injected into larvae of two species of predatory mites (Acari: Phytoseiidae)*, 18 EXPERIMENTAL & APPLIED ACAROLOGY 301, 302 (1994).

63. *Id.*

64. *Id.*

65. See Hokanson, *supra* note 6, at 2–4 & tbl. 1.

66. Notice of Availability of Environmental Assessments and Findings of No Significant Impact, 61 Fed. Reg. 15,458 (Dep’t of Agric. Apr. 8, 1996).

67. *Id.* at 15,459.

68. *Id.* at 15,458.

69. *Pink Bollworm*, OXITEC, <http://www.oxitec.com/agriculture/our-products/pink-bollworm/> (last visited May 1, 2015).

70. Bill Grefenstette et al., *Pink Bollworm Eradication Plan in the U.S.*, APHIS (U.S.D.A. February 2009), https://www.aphis.usda.gov2Fplant/plant_health2Fplant_pest_info2Fcotton/cotton_pests/downloads/pbw-erad-plan2-09.pdf.

states in the southwestern United States and incorporates four methods of insect control: (1) mating disruption with pink bollworm sex pheromone (gossyplure); (2) planting of Bt transgenic cotton; (3) sterile insect technique; and (4) cultural control.⁷¹ In 2007, pink bollworms carrying a heritable fluorescent marker were released in Arizona cotton fields as part of a field test under the sterile insect control program.⁷² Sterilized moths containing the fluorescent transgene were developed in order to facilitate accurate monitoring in the field, which confers a benefit over traditional methods of tracking sterilized moths (e.g., the use of red dyes incorporated into the feed during larval development).⁷³ The transgenic pink bollworms, as developed by Oxitec, contain a DsRed2 fluorescent protein inserted into the organisms' genome and sterilized via gamma-irradiation.⁷⁴ As discussed previously for transgenic mosquitoes, the ultimate goal of this technique is to indirectly reduce the target insect population by encouraging breeding competition between wild-type and sterilized males.⁷⁵

APHIS issued permits for the field tests upon the finding of "no significant impact" in two Environmental Assessments and an Environmental Impact Statement.⁷⁶ In the first EA, APHIS addressed the use of moths carrying an EGFP marker in 3-acre field sites of cotton as part of APHIS's Center for Plant Health Science and Technology's (CPHST) efforts to eradicate the pink bollworm.⁷⁷ A FONSI was reached after APHIS determined that there would be no risk of introduction or dissemination of a plant pest into the environment.⁷⁸ Specifically, APHIS noted that the

71. *Id.*; see also *Transgenic Cotton*, http://ag.arizona.edu/pubs/general/resrpt1996/t_cotton.html (explaining the development of Bt cotton, i.e., cotton containing a toxin gene from *Bacillus thuringiensis*, and how it can be used to control insect populations).

72. *USDA Approves Release of Transgenic Pink Bollworm Moths on up to 120 Acres of Cotton in Arizona*, OXITEC (Apr. 26, 2007), <http://www.oxitec.com/usda-approves-release-of-transgenic-pink-bollworm-moths-on-up-to-120-acres-of-cotton-in-arizona/>.

73. Gregory S. Simmons et al., *Field Performance of a Genetically Engineered Strain of Pink Bollworm*, PLOS ONE 6(9): e24110, Sept. 13, 2011, at 1–2.

74. Simmons, *supra* note 73, at 7–9.

75. See Florida Keys Project, *supra* note 15.

76. Pink Bollworm, *supra* note 69.

77. Notice of Availability of an Environmental Assessment and Finding of No Significant Impact for Field Release of Genetically Engineered Pink Bollworm, 71 Fed. Reg. 20,068 (Apr. 19, 2006).

78. *Id.* at 20,069.

transgenic bollworm's fecundity was significantly lower than wild pink bollworms and that several redundant mitigation measures were in place to ensure that the genetically modified insects did not become established in the environment.⁷⁹ APHIS prepared an addendum to its first EA to reflect a new requested field test location and new testing conditions commensurate with the change.⁸⁰ APHIS maintained the FONSI previously associated with EA, as none of these proposed changes were found to raise new plant pest issues.⁸¹

Although a FONSI pursuant to an EA would not normally require the preparation of an EIS, APHIS (in conjunction with the EPA) prepared an EIS in order to document its decision to "permit the integration of genetically engineered insects into its plant pest control and eradication programs."⁸² In the EIS, APHIS specifically considered three alternatives to the introduction of transgenic bollworms: (1) maintaining current irradiation-based sterile insect technique via no action; (2) expanding the size, capacity, and diversity of existing programs; and (3) integrating genetically engineered insects into its plant pest control programs.⁸³ APHIS rejected the first alternative because the continuation of the standard approach would not "contribute to increased mitigation of present or future plant pest risks."⁸⁴ APHIS similarly rejected the second alternative because it would result in "higher program costs, greater mass-rearing facility construction, longer timeframes for development, and more extensive pest mitigation efforts than . . . the integration of genetically engineered insects into APHIS

79. *Id.*

80. Notice of Availability of an Addendum to Environmental Assessment and Finding of No Significant Impact for Field Release of Genetically Engineered Pink Bollworm, 71 Fed. Reg. 42,348, 42,349 (July 26, 2006).

81. *Id.* Although the EA only addresses the use of the EGFP marker, field test permits include insects carrying either EGFP or DsRed2 as the marker. *Cf.*, e.g., USDA Field Tests of GM Crops Permit 05-098-01r, INFORMATION SYSTEMS FOR BIOTECHNOLOGY, <http://www.isb.vt.edu/getRelDetail.aspx?bp=05-098-01r> (last visited May 1, 2015) (listing "Green fluorescent protein" as the associated gene and linking to an available EA), USDA Field Tests of GM Crops Permit 06-151-01r, INFORMATION SYSTEMS FOR BIOTECHNOLOGY, <http://www.isb.vt.edu/getRelDetail.aspx?bp=06-151-01r> (last visited May 1, 2015) (listing "DsRed, Green fluorescent protein" as the associated gene but not linking to an EA).

82. Notice of Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs; Record of Decision, 74 Fed. Reg. 21,314, 21,315 (May 7, 2009).

83. *Id.*

84. *Id.* at 21,316.

sterile insect technique programs.”⁸⁵ APHIS ultimately selected the integration of genetically modified insects into plant pest control programs because it allows for the most environmentally safe and efficient reduction of pests among the three alternatives.⁸⁶ For example, the integration approach has the potential to “decrease the need for insecticide applications, to decrease the need to produce both male and female insects for use in sterile insect releases, to increase production of males that are more competitive in mating than radiation-sterilized males, and to eliminate the need to use, operate, and maintain strong gamma radiation sources.”⁸⁷ In this same EIS, APHIS also approved the application of this technology to fruit fly control methods.⁸⁸

B. Regulation of Other Genetically Modified Animals under the FDA

In addition to the regulation of genetically modified insects by APHIS, other higher organisms have fallen under the regulatory jurisdiction of the FDA. As the Oxitec mosquitoes are presently pending regulatory approval as a new animal drug under the FDA, an examination of the extent of the FDA’s regulation over genetically modified animals can provide insight into the mosquitoes’ unique categorization. At present, two genetically engineered (GE) fish species— the AquAdvantage® Salmon and the GloFish®—have been the subject of regulatory consideration by the FDA.

So far, the FDA has declined to strictly regulate these transgenic fish because they are not intended for release into the wild, and there is little chance that these fish would become established in the U.S. environment even in the event of release. The FDA will likely regulate the Oxitec mosquitoes more heavily because Oxitec does intend to introduce the mosquitoes into the wild, and there is a high probability that the mosquitoes will have a large impact on the U.S. environment.

1. AquAdvantage® Salmon

The AquAdvantage® Salmon, developed by AquaBounty Technologies, is a product of the commercial aquaculture

85. *Id.*

86. *Id.*

87. *Id.* at 21,315.

88. *Id.*

industry.⁸⁹ This genetically modified Atlantic salmon contains genetic material from two other fish species—a growth hormone gene from the Chinook salmon and a “promoter” gene from the ocean pout.⁹⁰ The promoter gene acts as an “on switch” that causes the AquAdvantage® Salmon to produce enhanced quantities of growth hormone from the Chinook salmon gene.⁹¹ These transgenic elements cause the AquAdvantage® Salmon to reach market size in about half the amount of time ordinarily required of Atlantic salmon.⁹² In addition to its obvious market advantage, the AquAdvantage® Salmon also provides an environmentally sustainable alternative to current farmed salmon.⁹³ The transgenic salmon are raised entirely in land-based facilities located near major consumer markets, which reduces the environmental impact typically associated with both coastal area salmon farming and long-distance salmon transportation.⁹⁴ The objective of this technology is to help meet the growing demand for high quality seafood while minimizing the depletion of wild fish stocks.⁹⁵

The AquAdvantage® Salmon is presently undergoing review by the FDA as the first genetically modified animal to enter the U.S. food supply.⁹⁶ In December 2012, the FDA issued a preliminary FONSI pursuant to an EA for a New Animal Drug Application (NADA) encompassing the genetically engineered salmon.⁹⁷ In the draft EA, the FDA determined that (1) there would be little likelihood of escape of the salmon from the farming facilities in Canada and Panama; (2) that the salmon would be unlikely to survive if they did escape confinement; (3) that the salmon would be unlikely to effectively reproduce and become established in the environment in the event of escape; and (4) that there would be no expected effects to the environment of the United States if the salmon did escape their facilities in Canada

89. *Products*, AQUABOUNTY TECHNOLOGIES, <http://aquabounty.com/company/products/> (last visited May 1, 2015).

90. *Id.*

91. *Products*, *supra* note 89.

92. *Id.*

93. *Id.*

94. *Id.*

95. *Aquaculture Market*, AQUABOUNTY TECHNOLOGIES, <http://aquabounty.com/aquaculture-market/> (last visited May 1, 2015).

96. Andrew Pollack, *Engineered Fish Moves a Step Closer to Approval*, N.Y. TIMES, Dec. 21, 2012, at B1.

97. Notice of Draft Environmental Assessment and Preliminary Finding of No Significant Impact Concerning a Genetically Engineered Atlantic Salmon, 77 Fed. Reg. 247 (Dec. 26, 2012).

and Panama.⁹⁸ Accordingly, the FDA issued a preliminary FONSI for the approval of the NADA and preliminarily determined that no EIS would be prepared.⁹⁹ Although the FDA initially announced a 60-day public comment period for the draft EA and preliminary FONSI, the agency later extended the comment period through April 26, 2013.¹⁰⁰ Incredibly, more than two decades have now passed since AquaBounty first approached the FDA about commencing the approval process for the genetically modified salmon.¹⁰¹

2. GloFish®

GloFish® are a popular category of aquarium fish that are microinjected with DNA from fluorescent jellyfish or sea anemones during the embryonic stage.¹⁰² The introduction of these foreign fluorescent protein genes allows the fish to glow red, green, orange, blue, purple, or pink without the aid of dyes or color injections.¹⁰³ Although the current use of GloFish® is focused on the pet trade, these fish were initially bred to help detect environmental pollutants.¹⁰⁴ Fluorescent fish have also been broadly used as model organisms in scientific studies of genetics, molecular biology, and vertebrate development, and these fish have been specifically used by biomedical scientists to better understand cellular mechanisms of disease and development, cancer, and gene therapy.¹⁰⁵

98. FDA, DRAFT ENVIRONMENTAL ASSESSMENT FOR THE AQUADVANTAGE® SALMON 98-99 (2012), <http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM333102.pdf>.

99. FDA, PRELIMINARY FINDING OF NO SIGNIFICANT IMPACT FOR THE AQUADVANTAGE® SALMON 5 (2012), <http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/UCM333105.pdf>.

100. Notice of Draft Environmental Assessment and Preliminary Finding of No Significant Impact Concerning a Genetically Engineered Atlantic Salmon; Extension of Comment Period, 78 Fed. Reg. 10,620, 10,620-21 (Feb. 14, 2013).

101. Emily Anthes, *Don't Be Afraid of Genetic Modification*, N.Y. TIMES, Mar. 9, 2013, at SR4.

102. GloFish FAQ, GLOFISH, <http://www.glofish.com/about/faq/> (last visited May 1, 2015).

103. *Id.*

104. *Id.*

105. *Id.*

In 2003, the FDA acknowledged the potential need for regulation of this transgenic fish.¹⁰⁶ But in an extremely succinct statement, the FDA ultimately declined to impose regulations over the fishes' sale in the pet trade because the fish were not being used for food purposes and did not appear to pose any more of an environmental risk than their long-sold unmodified counterparts.¹⁰⁷ In *International Center for Technology Assessment v. Thompson*, a group of technology oversight and environmental advocacy organizations unsuccessfully attempted to challenge the FDA's refusal to regulate the transgenic fish by claiming such a refusal violated the Food, Drug and Cosmetic Act (FDCA), NEPA, and the Endangered Species Act (ESA).¹⁰⁸ In denying the plaintiffs' motion to alter or amend dismissal of these claims, the court determined that the FDA's refusal to regulate GloFish® (or any particular genetically engineered animal) was not a "major federal action" triggering NEPA requirements or an "agency action" triggering ESA requirements.¹⁰⁹ With respect to the NEPA and ESA claims, the court noted that the standard for a "major federal action" and "agency action" are much the same and that agency inaction did not equate to "agency action" under these statutes.¹¹⁰

V. PROPOSED REGULATION OF GENETICALLY MODIFIED MOSQUITOES AS AN ANIMAL DRUG

The FDA defines a new animal drug, in part, as "any drug intended for use in animals other than man, including any drug intended for use in animal feed but not including the animal feed, the composition of which is such that the drug is not generally recognized as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling of the drug."¹¹¹ The FDCA prohibits the sale of a new animal drug in interstate commerce unless the drug is the subject of an approved new animal drug application (NADA) or a conditional approval

106. FDA, STATEMENT REGARDING GLOFISH, (2003), <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm413959.htm>.

107. *Id.*

108. *Int'l Ctr. For Tech. Assessment v. Thompson*, 421 F. Supp.2d 1, 4 (D.D.C. 2006).

109. *Id.* at 9–11.

110. *Id.* at 10–11.

111. *New Animal Drug Applications*, *supra* note 8 (citing 21 U.S.C. § 321(v)).

pursuant to 21 U.S.C. § 360ccc.¹¹² Although new animal drugs generally must comply with these provisions, unapproved investigational new drugs may be exempt from these requirements if the drug fits within the criteria listed in 51 C.F.R. § 511.¹¹³

In 2009, the FDA published guidance on the regulation of genetically engineered animals containing heritable recombinant DNA (rDNA) constructs (i.e., constructs that may be passed through the lineage of a genetically modified animal).¹¹⁴ Under this guidance, the FDA considers the FDCA definition of a “drug” to be met by an “rDNA construct in a GE animal that is intended to affect the structure or function of the body of the GE animal, regardless of the intended use of products that may be produced by the GE animal”¹¹⁵ Although the regulated article is technically the rDNA construct within the animal, the FDA frequently refers to the regulation of the whole animal as a sort of shorthand.¹¹⁶ Any animals derived from the same transformation event (e.g., animals containing the rDNA construct as a result of breeding of the genetically modified animal) are considered to contain the same regulated article and are thus evaluated under a single NADA.¹¹⁷ In order to demonstrate effectiveness of the regulated article during the NADA approval process, one would need to show that the genetically modified animal had the claimed altered characteristic.¹¹⁸ Additionally, for commercially available genetically engineered animals, sponsors will subsequently need to demonstrate that the “construct and/or phenotype are stably maintained in a representative sample of animals” following use in commerce.¹¹⁹ Although all such genetically modified animals would be subject to premarket approval requirements, the FDA has decided not take investigational new animal drug (INAD) or NADA enforcement actions with respect to certain genetically modified animals.¹²⁰ Exempt animals include: “(1) GE animals of non-food-species that are regulated by other government agencies

112. *Id.* (citing 21 U.S.C. §§ 331(a), 360b(a)).

113. *Id.*

114. FDA, GUIDANCE FOR INDUSTRY #187, REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS 3 (2015), <http://www.fda.gov/htmdownloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm113903.pdf>.

115. *Id.* at 6.

116. *Id.* at 7.

117. *Id.*

118. *Id.* at 13.

119. *Id.* at 7 (citing 21 C.F.R. § 514.1(b)(5)).

120. *Id.*

or entities . . . ; and (2) GE animals of non-food-species that are raised and used in contained and controlled conditions such as GE laboratory animals used in research institutions.”¹²¹

Because the transgenic mosquitoes developed by Oxitec contain a heritable rDNA construct that is designed to affect the animal’s structure or function (i.e., the DNA construct containing the fluorescent marker and lethal gene is designed to prevent to the production of viable offspring), the inserted rDNA construct would seem to fall squarely within the FDA’s definition of a “drug” under the FDCA. Additionally, because this construct is being used in animals rather than humans and has not yet been evaluated for safety and efficacy under a NADA, the construct further comes under the definition of a “new animal drug.” The transgenic mosquitoes containing the construct also do not qualify for a GE animal exemption, as the mosquitoes are not regulated by other government agencies and are not for use in a controlled or contained environment.

Although it may seem curious that a genetically modified insect with the potential to affect its own wild population would fall outside of the jurisdiction of the EPA or APHIS, the limitations imposed by the Framework and the underlying statutes demonstrate why these mosquitoes do not come within the proper regulatory jurisdiction of either of these agencies. First, the EPA’s regulatory jurisdiction is limited to certain microorganisms and pesticides.¹²² Mosquitoes are not microorganisms (e.g., bacteria, yeasts, simple fungi, algae, protozoans, and certain other microscopic organisms).¹²³ Mosquitoes would also not seem to fall within the EPA’s definition of a pesticide, which excludes biological control agents such as ladybugs and other insect predators.¹²⁴ Second, APHIS’s regulatory jurisdiction is focused on animal biologics, plants, seeds, plant pests, animal pathogens, and “regulated articles.”¹²⁵ Although mosquitoes could likely be considered an animal pest and may harbor some animal pathogens

121. *Id.*

122. See SUTTON, *supra* note 5, at 37.

123. *Vocabulary Catalog Thesaurus of Terms Used in Microbial Risk Assessment*, EPA http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=MRAThesaurus&filterTerm=microorganism&filterMatchCriteria=Contains (last updated Sept. 2007).

124. *Basic Information about Pesticide Ingredients*, EPA, <http://www.epa.gov/ingredients-used-pesticide-products/basic-information-about-pesticide-ingredients> (last updated Nov. 5, 2015).

125. *Id.*; see also Coordinated Framework, *supra* note 28.

(e.g., dengue fever virus and chikungunya virus), the mosquitoes themselves also do not fit neatly within any of the defined biological product categories regulated by APHIS. Accordingly, the genetically modified mosquitoes would appear to cleanly escape regulation by EPA or APHIS under the present Framework and the associated legislation.

VI. CONCLUSIONS AND FUTURE DIRECTIONS

An analysis of the regulatory framework applicable to genetically modified insects reveals a confusing array of statutes, regulations, and official policies. While some insects may be regulated under the authority of APHIS due to their agricultural implications, other insects may fall under a more general net of regulation by the FDA. Additionally, it is conceivable that some genetically modified insects might slip through the cracks of regulation altogether, similar to the situation involving the GloFish®. Of the three major agencies involved in the regulation of biotechnology, it would appear that the EPA has the least amount of primary regulatory authority over insects released into the wild. EPA's biotechnology product and research jurisdiction is largely limited to certain microorganisms and biologically-based pesticides (e.g., pheromones and microbial compositions), which would not encompass insects. In contrast, APHIS appears to have broad regulatory authority over both the resulting transgenic insect and the specific incorporated genetic material if either is amenable to categorization as a "plant pest." The transgenic insects most likely to fall under the jurisdiction of APHIS would thus include those insects identified as plant pests (such as the pink bollworm) or those that contain genetic material derived from plant pests. Among the major regulatory agencies identified in the Framework, the FDA would appear to have the broadest potential to regulate genetically modified insects. The FDA's authority to regulate transgenic insects stems from the agency's ability to regulate drugs, which includes genetic constructs that affect the structure or function of an animal. Historically, however, the FDA has been reluctant to regulate animals that do not enter the food supply and that do not pose an apparent risk to public health.

Although the Framework was intended to establish the basic regulatory channels for genetically modified organisms, there seems to be current widespread confusion about matching a transgenic animal to the appropriate regulatory agency. The developer of the GloFish®, for example, contacted the EPA,

USDA, and the Fish and Wildlife Service before finally turning to the FDA.¹²⁶ Although the FDA ultimately declined to regulate this animal, at least one state (California) has independently prohibited the sale of GloFish® within its borders under its own NEPA-like statute.¹²⁷ In the case of Oxitec, the present mosquito technology was pending before the USDA for 18 months before the agency determined that it did not have regulatory jurisdiction.¹²⁸

Such uncertainties and administrative delays may have the unfortunate effect of turning biotechnology companies away from the development of transgenic animal technologies. In response to the drawn-out regulatory process involving the AquaAdvantage® Salmon, for example, one chief official at another animal biotechnology company stated “[t]he AquaBounty example has [made our] company very skeptical about how much investment to pour into the U.S. regulatory process.”¹²⁹ Additionally, as with the prohibited sale of GloFish® in California, such regulatory hesitation at the federal level may indirectly exacerbate localized regulatory hurdles by inviting individual states to develop their own particularized regulatory requirements.

Given these present issues, the time is ripe to amend the Framework and the underlying legislation to provide some further clarity regarding the regulatory process. One possible approach would be to amend the applicable statutes to better explain the jurisdiction of various government agencies. For example, the government might explicitly state that the FDA has original jurisdiction over all genetically modified organisms via the FDCA absent some other clearly delineated criteria.

Additionally, amendments to these statutes could better clarify whether it is the genetic alteration or the resulting organism that is the true target of regulation. In the draft EA for the AquaAdvantage® Salmon, for example, the FDA indicated that the NADA was for the approval of the “integrated α -form of the opAFP-GHc2 gene construct at the α -locus in the EO-1 α line of the Atlantic salmon under the conditions of use specified in the

126. Editorial, *The One that Got Away*, 22 NATURE BIOTECHNOLOGY 1 (2004).

127. See *The New Industry of Manufacturing Pets*, CTR. FOR GENETICS & SOC’Y (Apr. 18, 2005), <http://www.geneticsandsociety.org/article.php?id=467>.

128. Joe Palca, *Biotech Firms Caught In Regulatory No Man’s Land*, NPR (Jan. 2, 2012, 12:02 AM), <http://www.npr.org/2012/01/02/144330629/biotech-firms-caught-in-regulatory-no-mans-land>.

129. Heidi Ledford, *Transgenic Salmon Nears Approval*, 297 NATURE 17, 17–18 (2013) (quoting Mark Walton, chief marketing officer at Recombinetics).

application.”¹³⁰ However, the document later indicates that the application pertains to the approval of the “AquAdvantage® Salmon” for ease of reference.¹³¹ Because it is unclear how the animal could ever be separated from its underlying genetic material, a classification scheme based on the end-product rather than the specific genetic alteration might present a more workable system of regulation. Accordingly, if the regulatory agency were explicitly authorized to regulate the corresponding transgenic animal, instead of the integrated form of the genetic construct, this might help to further clarify the regulatory process.

Another potential solution would be to establish a central regulatory authority that conducts an initial assessment of genetically modified organisms seeking regulatory approval and redirects the products to the appropriate governmental agency. This approach has previously been proposed by others, as one commentator suggested that the United States establish a Supreme Office of Transgenic Oversight in response to the unregulated status of the GloFish®.¹³² Such an agency would be responsible for taking a first look at all transgenic products (or perhaps all products of genetic manipulation) and then channeling them to the appropriate agency.¹³³ This office could also assume responsibility for the regulation of any awkward product categories that escape the jurisdiction of the current regulatory agencies.¹³⁴

A comparable method is currently used in the European Union (EU), as explained in the European Commission’s “Users Guide to European Regulation in Biotechnology” (the Guide). The rationale for the EU’s community strategy approach in the Guide, in part, is as follows: “Uncertainty about regulatory approaches has resulted in insufficient resources being put into research and development (R&D). While it remains legitimate for Member States to pursue certain policies of their own in accordance with the ‘subsidiarity principle’—under which decisions are taken as closely as possible to the citizen—it is sensible for the Community to play a coordinating role, providing a degree of coherence to policies and legislation.

130. *Draft Environmental Assessment*, FDA, 1 (May 4, 2012), <http://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/htmGeneticallyEngineeredAnimals/UCM333102.pdf>.

131. *Id.*

132. *The One that Got Away*, *supra* note 126.

133. *Id.*

134. *Id.*

The Strategy for Europe is key to this process, establishing a common vision and guiding principles and objectives".¹³⁵

The Guide goes on to provide a step-by-step process for obtaining approval for both commercial and noncommercial deliberate releases of genetically modified organisms under Directive 2001/18/EC.¹³⁶ Additionally, the Guide specifically lists the competent state-level authorities for each of the member states.¹³⁷ Although European countries are often criticized for imposing overly burdensome regulations on biotechnology products,¹³⁸ perhaps adopting a similar centralized authority to oversee the regulation of transgenic animals in the United States could help streamline the current regulatory process. Such streamlined regulation might, in turn, incite organizations presently deterred by the disorganized regulatory framework to pursue further development and commercialization of biotechnology products.

Although the regulatory process for genetically modified insects remains somewhat murky, insight into the specific characteristics of an organism that dictate a specific regulatory path can be elucidated by careful study of the applicable statutes, regulations, and guidance documents. Because each new transgenic organism seems to present a new regulatory dilemma, however, adding amendments to the existing laws or the establishment of a central regulatory authority may help to streamline this process. In the absence of such changes, the United States may eventually find it difficult to maintain its position as a world leader in the arena of biotechnology.

135. European Comm'n, Contract no. FIF.2004 0828, USERS GUIDE TO EUROPEAN REGULATION IN BIOTECHNOLOGY 15.

136. *See id.* at 67-73.

137. *See id.* at 74-90.

138. *See The One That Got Away*, *supra* note 126.