# Mismatched Regulation: Genetically Modified Mosquitoes and the Coordinated Framework for Biotechnology

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*Under the Coordinated Framework for Regulation of Biotechnology, the federal government has long relied on a patchwork of laws to oversee genetically modified organisms. The Framework was criticized as inadequate from the outset, and new techniques for manipulating genes or editing entire genomes offer further challenges to the Framework's adequacy and consistency. The federal government's response to the proposed release of a genetically modified mosquito offers a useful case study regarding the shortcomings of the Framework. Ideally, the decision-making process for biotechnologies would assess and manage relevant risks, acknowledge and address sources of uncertainty and ignorance, engage stakeholders and the public and attempt to reflect their values, and build public confidence that the process is effective and legitimate.*

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For over thirty years, the Coordinated Framework for Regulation of Biotechnology ("Coordinated Framework" or "Framework") has guided federal regulation of biotechnology products. The Framework relies on a patchwork of laws to allocate oversight of biotechnology products among federal regulatory agencies. The Obama Administration's 2017 update to the Framework offered the potential to account for new technological developments and to respond to criticisms of the Framework.

However, as illustrated by the government's response to the proposed experimental release of a genetically modified mosquito in the Florida Keys, this potential remains largely unrealized. Oxitec, a British biotechnology company, has genetically modified a mosquito so that male mosquitoes pass on a lethal genetic trait to any offspring.[1] The Food and Drug Administration ("FDA") evaluated Oxitec's mosquito as an investigational new animal drug, determined that the proposed field trial would not significantly impact the environment, and turned the matter over to local authorities to decide whether to proceed with the release. While the federal government took these actions before finalizing the Framework update, the update did not significantly change the Framework's basic approach. As new techniques for manipulating and editing genes offer the prospect of additional genetically modified organisms ("GMOs"), the federal government's handling of the Oxitec mosquito offers a useful case study regarding the inadequacy of current legal frameworks for new biotechnologies. Ideally, the decision-making process for such technologies would assess and manage relevant risks, acknowledge and address sources of uncertainty and ignorance, engage stakeholders and the public and attempt to reflect their values, and build public confidence that the process is effective and legitimate.

Part I of this Article describes the Oxitec mosquito as well as other genetically modified mosquitoes that scientists are developing with recently introduced gene manipulation techniques. Part II discusses the Coordinated Framework and explains the specific regulatory process applied to Oxitec's proposed field trial. Part III critiques that process and considers how decision-making for new biotechnologies might be improved.

[1] Robert Kolker, *Florida's Feud over Zika-Fighting GMO Mosquitoes*, BLOOMBERG BUSINESSWEEK (Oct. 6, 2016), https://www.bloomberg.com/features/2016-zika-gmo-mosquitos.

## I. GENETICALLY MODIFIED MOSQUITOES: PRESENT AND FUTURE

The yellow fever mosquito (*Aedes aegypti*) spreads Zika, dengue fever, and other diseases, making its control essential.[2] Because only female mosquitoes bite, only females are able to transmit disease.[3] Conventional means of control include spraying pesticides, eliminating standing water, and wearing protective clothing.[4] Pesticide spraying can only reduce *A. aegypti* populations by about 50 percent because it can be difficult to reach the locations — in and near homes — where the species prefers to live.[5] In addition, pesticides may result in toxic exposures to humans and the environment, and their frequent use can contribute to pesticide resistance.[6] Other methods of mosquito control, such as eliminating standing water or putting up window screens, are relatively simple and inexpensive but can require coordinated, labor-intensive efforts.[7]

### A. *Oxitec's Mosquito*

To control *A. aegypti* populations more effectively, Oxitec has developed a genetically modified mosquito that is intended to mate with wild mosquitoes and produce offspring that will not survive to adulthood.[8] Oxitec developed its genetically modified mosquito strain by micro-injecting mosquito eggs with recombinant DNA containing a gene that causes lethality in the absence of the antibiotic tetracycline.[9] Before releasing its mosquitoes into the environment, Oxitec mechanically screens mosquito pupae to remove females.[10] Large numbers of adult males containing the lethal gene are then released, in the expectation that they will breed with wild females and produce

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[2] *See* CTR. FOR VETERINARY MED., ENVIRONMENTAL ASSESSMENT FOR INVESTIGATIONAL USE OF *AEDES AEGYPTI* OX513A 18 (2016) [hereinafter EA].

[3] *See id.* at 16.

[4] WILSON CTR., THE DNA OF THE U.S. REGULATORY SYSTEM: ARE WE GETTING IT RIGHT FOR SYNTHETIC BIOLOGY? 15 (2015).

[5] *Id.*

[6] *See* EA, *supra* note 2, at 21; Adrienne LaFrance, *Genetically Modified Mosquitoes: What Could Possibly Go Wrong?*, ATLANTIC (Apr. 26, 2016), https://www.theatlantic.com/technology/archive/2016/04/genetically-modified-mosquitoes-zika/479793.

[7] *See* LaFrance, *supra* note 6.

[8] Oxitec's approach builds on a conventional method of insect population control, the Sterile Insect Technique. Under the Sterile Insect Technique, large numbers of sterile males are released repeatedly with the intent that they will outcompete wild males in mating with wild females. *See* EA, *supra* note 2, at 21.

[9] *See id.* at 25-26; WILSON CTR., *supra* note 4, at 15-16.

[10] *See* EA, *supra* note 2, at 36.

offspring that cannot survive in the wild. Oxitec claims that repeated releases of its genetically modified mosquito can reduce mosquito populations by 90 percent.[11] However, because various factors affect disease transmission, it is uncertain whether a reduction in mosquito populations of that magnitude would be sufficient to prevent the spread of mosquito-borne diseases.[12] Indeed, in public statements, Oxitec has avoided making direct claims regarding disease control.[13]

Oxitec has conducted releases of its genetically modified mosquito in the Cayman Islands, Panama, Malaysia, and Brazil.[14] The first releases took place in the Cayman Islands, where Oxitec carried out a small field trial in 2009 and a broader trial in 2010.[15] Oxitec claimed that the latter trial, in which ten transgenic males were released for every wild male present, reduced mosquito populations by 80 percent.[16] Oxitec's most extensive efforts have taken place in Brazil, where the company has conducted a series of field trials since 2011.[17] The most prominent of these efforts occurred in Piracicaba, a city where the company released nearly thirty million mosquitoes in an area with 5,000 residents.[18] The apparent success of these efforts in reducing mosquito populations, combined with growing concerns about Zika, led to an expansion of the release to an area containing up to 60,000 residents.[19] Oxitec is now seeking government approval to market its mosquitoes commercially in Brazil.[20]

For several years, Oxitec has sought to move forward with a field trial in the United States. In this field trial, planned for the Florida

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[11] *United States*, OXITEC, http://www.oxitec.com/programmes/united-states (last visited Mar. 13, 2017).

[12] *See* LaFrance, *supra* note 6.

[13] *See id.*

[14] EA, *supra* note 2, at 20.

[15] *See* Martin Enserink, *GM Mosquito Trial Alarms Opponents, Strains Ties in Gates-Funded Project*, 330 SCIENCE 1030, 1030 (2010).

[16] *See id.*

[17] *See* Kelly Servick, *Brazil Will Release Billions of Lab-Grown Mosquitoes to Combat Infectious Disease. Will It Work?*, SCIENCE (Oct. 13, 2016, 9:00 AM), http://www.sciencemag.org/news/2016/10/brazil-will-release-billions-lab-grown-mosquitoes-combat-infectious-disease-will-it.

[18] *See* Alexandra Sifferlin, *The War Against Mosquitoes: A Tale from the Front Lines*, TIME (2016), http://time.com/the-war-against-mosquito.

[19] *See id.*

[20] *See id.* Brazil's health regulatory agency recently classified Oxitec's mosquito as a novel medical technology that requires the agency's approval prior to commercialization. Reinaldo Jose Lopes, *Why Transgenic Insects Are Still Not Ready for Prime Time*, NATURE (Apr. 22, 2016), http://www.nature.com/news/why-transgenic-insects-are-still-not-ready-for-prime-time-1.19804.

Keys, the company intends to evaluate the ability of its genetically modified mosquitoes to mate with local wild mosquitoes, assess the survival of offspring from such mating, and determine the efficacy of its technique in suppressing mosquito populations.[21]

Various concerns have been expressed regarding the effectiveness of Oxitec's approach and the potential unintended consequences of any field trial. First, some genetically modified adult female mosquitoes are likely to be present in the environment as a result of a field trial.[22] As Oxitec admits, its methodology is not flawless. Up to one of every 500 released mosquitoes would be female since the mechanical process of sorting male and female pupae is imperfect.[23] Moreover, while most offspring resulting from the mating of genetically modified males and wild females will die before reaching adulthood, a small percentage may survive even in the absence of tetracycline.[24] In addition, trace amounts of tetracycline in sewage treatment plant discharge and agricultural residues could enable genetically modified mosquitoes to survive.[25] Although each of the aforementioned factors would result in the presence of genetically modified adult females in the wild, FDA concluded that any bites from these mosquitoes would pose no additional toxic or allergenic risks.[26]

There are other concerns as well. The effectiveness of Oxitec's efforts could be reduced by natural selection. If wild females develop a mating preference for wild males, the release of genetically modified males may do little to reduce mosquito populations.[27] Moreover, even if Oxitec's technique suppresses *A. aegypti* populations, its effects on disease transmission rates are uncertain. Suppression of *A. aegypti*

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[21] *See* EA, *supra* note 2, at 16.

[22] *See id.* at 91.

[23] *See id.* at 16, 91.

[24] *See id.* at 91 (noting lack of complete penetrance of lethality trait).

[25] *See* Wenonah Hauter, Food & Water Watch, Comment Letter on Draft Environmental Assessment and Preliminary Finding of No Significant Impact Concerning Investigational Use of Oxitec OX513A Mosquitoes; Availability (Docket No. FDA-2014-N-2235), (May 13, 2016) [hereinafter FWW] (discussing pesticidal use of tetracycline to treat citrus-greening disease, as well as residual tetracycline in sewage as a result of human use); Dana Perls, Friends of the Earth, Comments on the Food and Drug Administration's Draft Environmental Assessment and Preliminary Finding of No Significant Impact for the Release of Genetically Engineered Mosquitoes as an Investigational New Animal Drug (Docket No. FDA-2014-N-2235), at 3 (May 13, 2016) [hereinafter FOE]. The use of tetracycline to raise GM mosquitoes could contribute further to the problem of antibiotic resistance, though Oxitec claims the quantity used is small compared to other uses. *See* Kolker, *supra* note 1.

[26] *See* EA, *supra* note 2, at 92-97.

[27] *See* Lopes, *supra* note 20.

populations might open up an ecological niche for other, more invasive or harmful mosquito species.[28] Other unintended consequences from release could include the mutation of genetically modified mosquitoes — or the viruses and microorganisms they carry — into more virulent pests.[29] However, experts suggest it is unlikely that any mutation would make things worse, particularly because the genetic modification is designed not to be passed on to multiple generations.[30] Indeed, bioethicist Arthur Caplan contends that "ignorance, distrust, fear of the unknown, and fear of prior efforts to use biology to combat pests" — rather than legitimate scientific concerns — are driving public resistance.[31]

### *B. More Genetically Modified Mosquitoes on the Way?*

Oxitec is not alone in its efforts to develop genetically modified mosquitoes. Whereas Oxitec relied on conventional recombinant DNA techniques to develop its mosquito, scientists working on other types of genetically modified mosquitoes also are employing newer genome editing techniques. Much of their attention focuses on gene drives, which are "systems of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced."[32] Operating in a manner contrary to the Mendelian rules of inheritance — under which offspring have only a 50 percent chance of inheriting a particular gene from a parent — gene drives allow stretches of DNA to be passed by a parent organism to virtually all its offspring.[33] Over the course of multiple generations, gene drives can spread a trait rapidly through a population.[34] Scientists have studied naturally occurring gene drives for some time, but until

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[28] *See* EA, *supra* note 2, at 116; FOE, *supra* note 25, at 2; Sifferlin, *supra* note 18 (reporting remarks from University of Florida entomologist that the Asian Tiger Mosquito could benefit from successful efforts to reduce *A. aegypti* populations).

[29] *See* LaFrance, *supra* note 6.

[30] *See id.*

[31] *Id.* Negative impacts from the use of biological pest controls have included ecological disturbance and species extinction. *See* Francis G. Howarth, *Environmental Impacts of Classical Biological Control*, 36 ANN. REV. ENTOMOLOGY 485, 488-500 (1991).

[32] NAT'L ACAD. OF SCI., ENG'G & MED. ET AL., GENE DRIVES ON THE HORIZON: ADVANCING SCIENCE, NAVIGATING UNCERTAINTY, AND ALIGNING RESEARCH WITH PUBLIC VALUES 1 (2016) [hereinafter GENE DRIVES].

[33] *See id.* at 2, 16.

[34] *See id.* at 16 fig.1-2.

recently lacked the tools to design a functioning gene drive.[35] The development of the CRISPR-Cas9 gene editing technique offers the ability to insert, delete, or replace specific genes with precision, and specifically to insert genes for desirable traits into gene drives.[36]

Scientists have quickly recognized the potential value of gene drive technology to control the spread of mosquito-borne diseases. Gene drives might be used to cause sterility in mosquitoes, reduce mosquitoes' susceptibility to infection by the malaria parasite, or otherwise induce disease resistance in mosquito populations.[37] In each instance, scientists must first identify genes coding for a desirable trait, and then engineer those genes into gene drives.[38]

Oxitec's strain of mosquitoes is "self-limiting" in that the genetic modification is designed to disappear from the mosquito population.[39] With this technique, effective pest control will likely require periodic re-releases of genetically modified mosquitoes.[40] In contrast, the release of mosquitoes containing a gene drive represents a "self-sustaining" approach that could make an entire wild population transgenic after a single release.[41] Such a strategy of population replacement could allow a targeted species of mosquitoes to continue to serve its ecological function as a food source, while reducing or eliminating disease transmission.[42] However, any effects on mosquito populations — or on ecosystems — could be irreversible.[43] Unintended consequences could include reduced resistance among mosquitoes to infection, increased transmission of diseases other than

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[35] *See id.* at 12, 13 fig.1-1.

[36] *See id.*; Editorial, *Driving Test*, 524 NATURE 5 (2015) (commenting that CRISPR "makes gene drives much easier and could dramatically accelerate the timeline for a potential release").

[37] *See* GENE DRIVES, *supra* note 32, at 51-52; Valentino M. Gantz et al., *Highly Efficient Cas9-Mediated Gene Drive for Population Modification of the Malaria Vector Mosquito* Anopheles stephensi, 112 PROC. NAT'L ACAD. SCI. E6736-37, E6742 (2015).

[38] For a discussion of design criteria for gene drive systems, see Anthony A. James, *Gene Drive Systems in Mosquitoes: Rules of the Road*, 21 TRENDS PARASITOLOGY 64, 65-66 (2005). *See also* Kenneth A. Oye et al., *Regulating Gene Drives*, 345 SCIENCE 626, 626-27 (2014) (discussing environmental and security aspects of gene drives).

[39] *See* WORLD HEALTH ORG., GUIDANCE FRAMEWORK FOR TESTING OF GENETICALLY MODIFIED MOSQUITOES 3-4 (2014) [hereinafter WHO].

[40] *Id.*

[41] *See id.* at 4-5; James, *supra* note 38, at 64; Kevin M. Esvelt et al., *Concerning RNA-Guided Gene Drives for the Alteration of Wild Populations*, EMERGING TECH. 3 (July 17, 2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117217/pdf/elife-03401.pdf.

[42] *See* David B. Resnik, *Ethical Issues in Field Trials of Genetically Modified Disease-Resistant Mosquitoes*, 14 DEV. WORLD BIOETHICS 37, 39 (2014).

[43] *See* GENE DRIVES, *supra* note 32, at 7; Servick, *supra* note 17.

the targeted disease, or evolution of more virulent pathogens.[44] The prospect of irreversible and uncertain consequences will likely give pause to the public and to regulators, who also may have to grapple with unintended transfer of genes to other populations or species, ecological effects that cross political boundaries, and efforts to mitigate unintended consequences.[45]

## II. THE REGULATORY RESPONSE

The federal regulatory response to Oxitec's proposed field trial has played out under a longstanding policy established by the Coordinated Framework for Regulation of Biotechnology. Pursuant to that policy, the government has applied statutes and regulations that were not developed with GMOs in mind, straining and stretching those legal authorities.

### A. *The Coordinated Framework for Biotechnology*

Established under President Ronald Reagan, the Coordinated Framework sets out the general federal policy for evaluating GMOs.[46] The Coordinated Framework essentially applies a patchwork of pre-existing legal authorities to govern various biotechnology products. The Framework's reliance on pre-existing laws is premised on the notion that such laws are adequate to address biotechnology risks and "could provide more immediate regulatory protection and certainty for the industry" than any new legislation could.[47] Under the Framework, three agencies have primary oversight responsibilities: the Animal and Plant Health Inspection Service ("APHIS") — an agency within the U.S. Department of Agriculture ("USDA") — oversees organisms that could pose plant pest risks; the Food and Drug Administration ("FDA") regulates safety and labeling of foods and drugs; and the Environmental Protection Agency ("EPA") reviews pesticidal substances.[48] Each agency's jurisdiction is determined largely by the intended use of a GMO.[49]

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[44] *See* Resnik, *supra* note 42, at 42.

[45] *See* GENE DRIVES, *supra* note 32, at 149-50; Bruce A. Hay et al., *Engineering the Genomes of Wild Insect Populations: Challenges, and Opportunities Provided by Synthetic* Medea *Selfish Genetic Elements*, 56 J. INSECT PHYSIOLOGY 1402, 1404 (2010).

[46] Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23302 (1986) [hereinafter Coordinated Framework] (Notice).

[47] *Id.* at 23303.

[48] *Id.*

[49] *Id.* at 23304.

A 1992 update to the Framework reaffirmed that federal oversight "focuses on the characteristics of the biotechnology product and the environment into which it is being introduced, not the process by which the product is created."[50] In that update, the federal government defended the Framework's risk-based approach as a scientifically grounded means of ensuring safety while encouraging useful innovation.[51] Noting that the original Framework did not address how agencies should exercise discretion granted by relevant statutes, the update directed agencies to exercise oversight "only where the risk posed by the introduction is unreasonable."[52]

The Coordinated Framework has remained in place even as underlying technologies have changed. In 2015, the Obama administration ordered a further update to the Framework.[53] As the order recognized, scientific advances "have dramatically altered the biotechnology landscape" and "uncertainty about agency jurisdiction, lack of predictability of timeframes for review, and other processes" under the Framework can impose substantial burdens.[54] Finalized in January 2017, the latest update delineates federal agencies' regulatory responsibilities in greater detail, clarifies mechanisms for interagency communication and coordination, and offers a handful of case studies to guide product developers.[55] This update generally remains faithful to the core principles of the 1986 Framework, particularly in relying on existing legal authorities and a risk-centered approach.[56]

### B. *The Regulatory Process for Oxitec*

In theory, the Coordinated Framework allows each regulatory agency to apply its expertise to address a GMO's possible risks. For any particular GMO, APHIS can consider plant pest and animal

[50] Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57 Fed. Reg. 6753, 6753 (1992) [hereinafter 1992 Update] (Notice).

[51] *Id.* at 6755-56.

[52] *Id.* at 6753.

[53] Memorandum from John P. Holdren et al. for Heads of FDA, EPA, and USDA 2 (July 2, 2015), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf.

[54] *Id.*

[55] *See* MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS: FINAL VERSION OF THE 2017 UPDATE TO THE COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY 8-51 (2017), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf [hereinafter 2017 UPDATE].

[56] *See id.* at 7-8.

disease risks, FDA can examine health and safety risks arising from use of the GMO as a food or drug, and EPA can weigh pesticidal risks.[57] However, the Framework discourages multiple agencies from simultaneously exercising oversight, directing that "[t]o the extent possible, responsibility for a product use will lie with a single agency."[58] In addition, regulatory jurisdiction is less clear for GMOs whose properties do not fall within existing legal categories, such as Oxitec's mosquito. The genetically modified mosquito is not obviously a plant pest, pesticide, food, or drug.

To address the potential regulatory gap for such animals, FDA has asserted that it can regulate genetically modified animals pursuant to its new animal drug authority.[59] The Federal Food Drug & Cosmetic Act defines a new animal drug as "any drug that is intended for use for animals other than man."[60] "Drug" is defined to include "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals" and "articles . . . intended to affect the structure or any function of the body of man or other animals."[61] FDA views genetic material that is inserted into an animal's genome as a "new animal drug" if it is intended to affect the structure or function of the body of the animal.[62] Under federal law, a

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[57] *See* Coordinated Framework, *supra* note 46, at 23304.

[58] *Id.* at 23303. *But cf.* 2017 UPDATE, *supra* note 55, at 28 n.77 (explaining that the update, in contrast to the original Framework, does not rely on the concept of lead agencies "because the concept caused confusion and was mistakenly interpreted").

[59] *See* U.S. FOOD & DRUG ADMIN., NO. 187, GUIDANCE FOR INDUSTRY: REGULATION OF INTENTIONALLY ALTERED GENOMIC DNA IN ANIMALS 4-6 (2017), https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm113903.pdf [hereinafter 2017 GUIDANCE 187]; U.S. FOOD & DRUG ADMIN., NO. 187, GUIDANCE FOR INDUSTRY: REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE rDNA CONSTRUCTS 4-6 (2015), https://wayback.archive-it.org/7993/20161022003714/http:/www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf [hereinafter 2015 GUIDANCE 187]. To avoid duplicative regulation, FDA has expressed an intent to clarify the division of responsibilities between itself and other agencies with respect to genetically engineered animals and to refrain from enforcing new animal drug requirements for GMOs regulated by other government agencies. 2017 GUIDANCE 187 at 7 nn.9–10. In January 2017, FDA released draft guidance specifically addressing the division of regulatory responsibility over genetically modified mosquitoes. *See infra* text accompanying notes 99–101.

[60] 21 U.S.C. § 321(v) (2012).

[61] *Id.* § 321(g)(1).

[62] 2017 GUIDANCE 187, *supra* note 59, at 6; *see also* 2017 UPDATE, *supra* note 55, at 18. FDA's 2017 draft revision of GUIDANCE 187, which attempts to clarify the guidance's applicability to new genome editing technologies, similarly recognizes "altered genomic DNA" in an animal as a new animal drug. 2017 GUIDANCE 187, *supra*

new animal drug is "deemed unsafe" (and therefore may not be used) unless FDA has approved an application for a particular use.[63] Approval of a new animal drug requires demonstration of a drug's effectiveness based on substantial evidence.[64] Notwithstanding confidentiality rules applicable to new animal drug applications, FDA has expressed its intent "to seek input from experts and the public where there is significant public interest in an issue, and . . . [where] the public may have relevant data or information to contribute."[65]

Oxitec first approached the federal government in 2008 regarding its proposed field trial in the Florida Keys.[66] However, "confusion" and delay surrounded the question of which agency would exercise jurisdiction over the company's genetically modified mosquito.[67] Oxitec initially was told to submit its proposed trial to the USDA's Veterinary Services office.[68] After the USDA concluded that it could not regulate the mosquito under its authority over plant and animal pests,[69] Oxitec turned to FDA's Center for Veterinary Medicine, which regulates new animal drugs.

Rather than seeking full-scale approval of its genetically modified mosquito as a new animal drug, Oxitec framed its proposed trial as an "investigational new animal drug" ("INAD"). Under FDA regulations, INADs are subject to certain labeling and recordkeeping requirements,[70] but are exempt from the approval process applicable to new animal drugs.[71] In order to qualify as an INAD, a drug must be "intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and

note 59, at 7.

[63] 21 U.S.C. § 360b(a)(1) (2012).

[64] James T. O'Reilly & Katharine A. Van Tassel, 2 FOOD & DRUG ADMIN. § 16:10 (4th ed. 2017 Update).

[65] 2017 GUIDANCE 187, *supra* note 59, at 13; *see also* 2017 UPDATE, *supra* note 55, at 19 n.62.

[66] *See* Emily Waltz, *A Face-Lift for Biotech Rules Begins*, 33 NATURE BIOTECHNOLOGY 1221, 1221 (2015).

[67] GENE DRIVES, *supra* note 32, at 147, 149.

[68] Waltz, *supra* note 66.

[69] *Id.*

[70] 21 C.F.R. § 511.1(b)(1)–(10) (2017).

[71] 21 U.S.C. § 360b(a)(3) (2012). Typically, the establishment of an INAD file is the initial step in seeking approval of a new animal drug, and it serves as a means of corresponding with FDA during the drug development and approval process. *See* 2017 GUIDANCE 187, *supra* note 59, at 9-10; *From an Idea to the Marketplace: The Journey of an Animal Drug Through the Approval Process*, FDA, http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm (last visited Aug. 22, 2017).

effectiveness of animal drugs."[72] Investigational use presumes in vitro testing, lab animal research, or clinical research.[73] Though an INAD usually does not require FDA approval, FDA reviews the environmental impacts of an INAD under the National Environmental Policy Act ("NEPA").[74]

Whether Oxitec's field trial properly qualified for the INAD exemption is open to question. According to FDA, "the development of [genetically engineered] animals constitutes clinical investigation because it involves studying the effectiveness of the drug in the target species and the effects of the [rDNA construct] . . . on the animal containing it."[75] Oxitec's field trial is investigative in nature in that Oxitec seeks to evaluate the effectiveness of its genetically modified mosquito in the Florida Keys. However, the trial will take place outdoors, not in a clinical setting. Accordingly, at least one commenter objected that Oxitec's planned release "is akin to a market-trial," not a clinical trial, and therefore cannot be treated as an INAD.[76]

Notwithstanding these concerns, FDA processed Oxitec's proposal as an INAD and issued an environmental assessment ("EA") and finding of no significant impact ("FONSI"). FDA concluded that the field trial poses an "extremely low" probability of various human and animal health impacts, including toxic or allergenic effects, increased disease transmission, or transfer of the modified gene to other species.[77] FDA also deemed it "highly unlikely" that a permanent population of genetically modified mosquitoes would become established, or that the Oxitec mosquito would interbreed with other mosquito species.[78]

Issuance of the EA and FONSI appeared to complete federal involvement in Oxitec's efforts to proceed with a field trial. According

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[72] 21 U.S.C. § 360b(j).

[73] *See* 21 C.F.R. § 511.1(a), (b).

[74] *See* 21 C.F.R. § 511.1(b)(10); 2017 GUIDANCE 187, *supra* note 59, at 9, 13. NEPA requires that federal agencies prepare an environmental impact statement ("EIS") for major federal actions significantly affecting the quality of the human environment. 42 U.S.C. § 4332(2)(C) (2012). Agencies may be required to prepare an environmental assessment to provide sufficient evidence and analysis to determine whether to prepare an EIS. 21 C.F.R. § 25.40 (2017); 40 C.F.R. § 1508.9 (2017).

[75] 2017 GUIDANCE 187, *supra* note 59, at 10 (alteration in original).

[76] FWW, *supra* note 25, at 2.

[77] U.S. FOOD & DRUG ADMIN., FINDING OF NO SIGNIFICANT IMPACT IN SUPPORT OF A PROPOSED FIELD TRIAL OF GENETICALLY ENGINEERED (GE) MALE *AEDES AEGYPTI* MOSQUITOES OF THE LINE OX513A IN KEY HAVEN, MONROE COUNTY, FLORIDA UNDER AN INVESTIGATIONAL NEW ANIMAL DRUG EXEMPTION 3-6 (2016) [hereinafter FONSI].

[78] *Id.* at 6-7.

to FDA, "[i]t is now Oxitec's decision, together with its local partner, the Florida Keys Mosquito Control District ("FKMCD"), to determine whether and when to begin the proposed field trial at Key Haven."[79] Acknowledging the strong public interest in whether to proceed with such a trial, the FKMCD placed two non-binding referendums on the November 2016 ballot. In those referendums, Monroe County residents voted in favor of proceeding with a field trial, while residents of Key Haven — the community where the trials originally were slated to occur — rejected a similar measure.[80] The FKMCD then voted to proceed with a field trial in a location other than Key Haven, a move that may require FDA to reevaluate its health and environmental analysis.[81] Notably, the Florida Keys are not the only possible site for a U.S. field trial. Other jurisdictions have expressed interest in deploying Oxitec's mosquitoes,[82] and heightened concerns about Zika and other mosquito-borne diseases could prompt further interest.

## III. IMPROVING DECISION-MAKING ON EMERGING TECHNOLOGIES

Notwithstanding FDA "approval" of field testing and the local mosquito board's deference to the referendum results, the Oxitec decision-making process was less than ideal. Decision-making regarding emerging biotechnologies should assess and manage relevant risks, acknowledge and address sources of uncertainty, engage the public and attempt to reflect its values, and build public confidence that the process is effective and legitimate.[83] This Part

[79] Letter from Robert M. Califf, Comm'r of Food & Drugs, Food & Drug Admin., to Jimmy L. Morales, City Manager, City of Miami Beach (Oct. 19, 2016) (on file with City of Miami Beach, City Manager's Office).

[80] Greg Allen, *Florida Keys Approves Trial of Genetically Modified Mosquitoes to Fight Zika*, NPR (Nov. 20, 2016, 9:11 AM), http://www.npr.org/sections/health-shots/2016/11/20/502717253/florida-keys-approves-trial-of-genetically-modified-mosquitoes-to-fight-zika.

[81] *See id.*; Baylor Cherry, *When Will the Keys Begin Using Genetically Modified Mosquitoes to Fight Zika?*, WUFT (Mar. 28, 2017), https://www.wuft.org/news/2017/03/28/when-will-the-keys-begin-using-genetically-modified-mosquitoes-to-fight-zika.

[82] *See, e.g.*, Letter from Robert M. Califf to Jimmy L. Morales, *supra* note 79; Naomi Martin, *Genetically Modified Mosquitoes Could Kill Their Own Kind, Cut West Nile, Zika Risk*, DALL. MORNING NEWS (Apr. 10, 2017), https://www.dallasnews.com/news/dallas-county/2017/04/10/genetically-modified-mosquitoes-coming-houston-dallas-county-officials-hope-next (reporting that Harris County is seeking approval to test genetically modified mosquitoes in the Houston area and that Dallas County officials are exploring possible use of such mosquitoes).

[83] *See* GENE DRIVES, *supra* note 32, at 140 (suggesting desirable features of governance for gene drives, including thorough risk assessment that identifies sources of uncertainty; engagement of communities, stakeholders, and the broader public;

reflects on the Oxitec regulatory process and considers how decision-making for new biotechnologies might achieve these objectives more effectively.

### A. *Assessing and Managing Risk*

#### 1. Regulatory Jurisdiction

Managing risks is a primary purpose of government oversight of emerging technologies. However, the Coordinated Framework's ability to effectively manage new biotechnology advances and their risks remains questionable, notwithstanding the additional guidance provided by the recent Framework update. Public comments on the draft update expressed concerns regarding whether the Framework provides adequate coverage of biotechnology products derived from new gene editing and gene silencing techniques.[84] Commenters also sought further clarification regarding how specific products would be regulated.[85] Even after the update, the Framework's treatment of genetically engineered insects illustrates the continued potential for inconsistencies in regulation. As one commentator contended:

> Genetically engineered (GE) insects are regulated as "plant pests" by the US Department of Agriculture and as "new animal drugs" by the Food and Drug Administration. . . . Even new kinds of techniques that researchers have envisioned using gene drives are still essentially pesticidal techniques. . . . It would make most sense to write new regulations that would have the EPA review ALL techniques intended to work as

clear authority, responsibility, and methods for accountability; and oversight proportionate to the risks involved); *see also* Albert C. Lin, *The Missing Pieces of Geoengineering Research Governance*, 100 MINN. L. REV. 2509, 2548-52 (2016) (setting out legitimacy and effectiveness as essential characteristics of governance of geoengineering research).

[84] *See* 2017 UPDATE, *supra* note 55, at 61-62.

[85] *See, e.g.*, ConsumersUnion, Comments of Consumers Union to the Office of Science and Technology Policy on Clarifying Current Roles and Responsibilities Described in the Coordinated Framework for the Regulation of Biotechnology: Request for Public Comment Docket No. FDA-2015-N-3403 (Nov. 1, 2016) (letter shows incorrect year); Annie Tang Gutsche, DuPont, Comment Letter on Docket Number FDA-2015-N-3403: Clarifying Current Roles and Responsibilities Described in the Coordinated Framework for the Regulation of Biotechnology (posted Nov. 2, 2016).

> pesticidal products in the bodies of insects whether they are genetic constructs or bacterial infections.[86]

In the context of the present case, treating Oxitec's genetic modification of *A. aegypti* as a new animal drug makes little sense. The genetic modification does not aid in the "diagnosis, cure, mitigation, treatment or prevention of disease" in the mosquito species itself. Rather, the genetic modification is a form of pest control, and the environment and human health risks associated with the technology should be governed by EPA, which has expertise in managing such risks.

Even if one assumes FDA oversight to be appropriate, it is not obvious that such oversight belongs within FDA's Center for Veterinary Medicine ("CVM"), which manages new animal drugs. CVM typically regulates antibiotics and other drugs used to treat disease in animals.[87] By contrast, Oxitec's genetically modified mosquito is ultimately intended to mitigate disease in humans, not animals. Accordingly, the FDA branch responsible for overseeing human drugs, the Center for Drug Evaluation and Research ("CDER"), is arguably a more suitable locus for oversight.[88] FDA's decision to handle the mosquito through the CVM rather than the CDER suggests excessive deference to Oxitec's characterization of its product as a tool for controlling mosquito populations.

Does it matter whether one particular agency or another regulates a product, as long as it is subject to some government oversight? That it should not matter much, if at all, is an underlying assumption of the Coordinated Framework. The Framework attempts to fashion a uniform approach to biotechnology risk by calling for oversight "only where the risk posed . . . is unreasonable."[89] Furthermore, in providing that "[t]o the extent possible, responsibility for a product use will lie with a single agency,"[90] the Framework suggests that the fact of oversight is more important than whether that oversight adequately protects the public from relevant risks.

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[86] Jaydee Hanson, International Center for Technology Assessment, Comment Letter on Coordinated Framework for the Regulation of Biotechnology and Developing a Long-Term Strategy for the Regulation of the Products of Biotechnology (Nov. 1, 2016).

[87] *See What Is the Role of the Center for Veterinary Medicine (CVM) in FDA and What Does CVM Regulate?*, FDA, https://www.fda.gov/AboutFDA/Transparency/Basics/ucm193812.htm (last visited Aug. 16, 2017).

[88] *See* WILSON CTR., *supra* note 4, at 17, 21.

[89] 1992 Update, *supra* note 50.

[90] Coordinated Framework, *supra* note 46, at 23303.

The nature of oversight nonetheless may vary sharply depending on the regulatory authority involved. For one, different agencies possess different types of expertise. An agency lacking expertise on a subject can consult with other agencies having more specialized knowledge, of course.[91] In Oxitec's case, for instance, FDA consulted with EPA and the Centers for Disease Control and Prevention in the course of evaluating risks.[92] Notwithstanding input from other agencies, the responsible agency's decisions are likely to be colored by its own mission and culture.[93]

More fundamentally, the Framework's allocation of regulatory authority determines the legal procedures and criteria that govern a particular product. Consider the possible options for regulating a genetically modified insect. If FDA reviews the insect as a new animal drug, FDA would evaluate whether the drug is "safe and effective for its intended use" as an animal drug, including the validity of claims made by its sponsor.[94] If FDA reviews the insect as a human drug, the agency would conduct a more extensive inquiry to determine whether the drug is safe and effective for human use.[95] If the insect is regulated under the USDA's Plant Protection Act authority, the USDA would determine whether the insect "can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof . . . ."[96] Finally, EPA oversight of the insect under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") would focus on whether the insect "will perform its intended function [as a pesticide] without unreasonable adverse effects on the environment."[97] Each of these

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[91] *Cf.* J.R. DeShazo & Jody Freeman, *Public Agencies As Lobbyists*, 105 COLUM. L. REV. 2217, 2288-92 (2005) (discussing how Congress attempts to control agency discretion by enabling or mandating input by other agencies).

[92] *See* FONSI, *supra* note 77, at 2.

[93] *See* Eric Biber, *Too Many Things to Do: How to Deal with the Dysfunctions of Multiple-Goal Agencies*, 33 HARV. ENVTL. L. REV. 1, 44-45 (2009) (suggesting that a decision-making agency that receives information and advice from other agencies "can simply choose to ignore it").

[94] 21 U.S.C. § 360b (2012); 2017 UPDATE, *supra* note 55, at 19; 2017 GUIDANCE 187, *supra* note 59, at 11.

[95] 21 U.S.C. § 355(d) (2012); Jordan Paradise & Ethan Fitzpatrick, *Synthetic Biology: Does Re-Writing Nature Require Re-Writing Regulation?*, 117 PENN. ST. L. REV. 53, 66 (2012) (characterizing new drug application process for human drugs as "the most rigorous review of any FDA-regulated product"); *see also* 2017 UPDATE, *supra* note 55, at 20.

[96] 7 C.F.R. § 340.1 (2017) (defining "plant pest"); *see also* 7 U.S.C. § 7711(a) (2012) (authorizing Secretary of Agriculture to regulate plant pests); 2017 UPDATE, *supra* note 55, at 23-24.

[97] 7 U.S.C. § 136a(c)(5) (2012); 2017 UPDATE, *supra* note 55, at 10.

inquiries would differ substantially in terms of the information considered and the stringency of oversight.[98]

Apparently recognizing the anomalies that resulted from treating Oxitec's mosquito as a new animal drug, FDA issued draft guidance on the matter in the waning days of the Obama administration. The draft "Guidance for Industry: Regulation of Mosquito-Related Products" clarifies "that the phrase 'articles (other than food) intended to affect the structure or any function of the body of man or other animals' in the FD&C Act's drug definition . . . does not include articles intended to function as pesticides by preventing, destroying, repelling or mitigating mosquitoes for population control purposes."[99] The guidance specifically proposes to divide federal oversight of genetically modified mosquitoes between FDA and EPA as follows: FDA would regulate "[p]roducts intended to reduce the virus/pathogen load within a mosquito" and "[p]roducts intended to prevent mosquito-borne disease in humans or animals," whereas EPA would regulate "[p]roducts intended to reduce the population of mosquitoes (for example, by killing them at some point in their life cycle, or by interfering with their reproduction or development)."[100] Under this approach, Oxitec's genetically modified mosquito would be regulated by EPA as a pesticide rather than by FDA as a new animal drug.[101] Regulation as a pesticide would better reflect the fact that Oxitec's product is aimed at reducing mosquito populations, not at treating them. Moreover, the draft guidance is responsive to the suggestion that EPA, which has expertise in managing health and environmental risks, should regulate genetically modified mosquitoes that are intended as a form of pest control. However, it would leave in place FDA regulation of other genetically modified mosquitoes as "new animal drugs" without EPA oversight.

[98] *See* Michael J. Donovan, *Genetically Modified Insects: Why Do We Need Them and How Will They Be Regulated?*, 17 MO. ENVTL. L. & POL'Y REV. 62, 89-105 (2009) (discussing possible sources of regulatory authority and regulatory requirements that would apply under each source).

[99] U.S. FOOD & DRUG ADMIN., NO. 236, GUIDANCE FOR INDUSTRY: REGULATION OF MOSQUITO-RELATED PRODUCTS 5 (2017).

[100] *Id.*

[101] *See id.* at 6 n.5 (noting that pesticidal regulations would apply both to "traditional chemical product[s]" and to "a recombinant DNA construct or bacteria intended to reduce the population of mosquitoes").

2. Scope and Adequacy of Risk Assessment and Management

As noted above, the Coordinated Framework incorporates a "risk-based approach to regulation."[102] To identify and analyze potential environmental impacts, FDA and other agencies rely heavily on the NEPA process.[103] However, environmental impact assessment alone does not assure adequate analysis and management of relevant risks.

Notably, NEPA does not require that agencies perform an ecological risk assessment.[104] Ecological risk assessment involves the "use of probabilistic decision-making tools to evaluate the likely benefits and potential harms of a proposed activity on the wellbeing of humans and the environment, often under conditions of uncertainty."[105] A 2016 National Academy of Sciences ("NAS") report on gene-drive modified organisms highlights the lack of ecological risk assessment as a prominent shortcoming of the NEPA process. As the report urges, the use of ecological risk assessment could promote better decision-making and the creation of testable hypotheses.[106]

Ecological risk assessments are unlikely to be done if the law does not require them. The Oxitec EA, for example, contains only a qualitative discussion of ecological risks.[107] The document provides no quantitative estimates of risk, nor does it offer a quantitative assessment of the uncertainty associated with its qualitative risk conclusions.[108] Conducting an ecological risk assessment on the field release of Oxitec's mosquito would require significant resources, but would also generate a far more complete set of information for decision makers.[109]

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[102] 2017 UPDATE, *supra* note 55, at 8.

[103] *See, e.g.*, 2017 UPDATE, *supra* note 55, at 18 (noting that NEPA compliance is required prior to market approval of genetically modified animals under new animal drug authority); *id.* at 16 (stating that "[f]ood additive approvals are also subject to [NEPA] requirements"); *id.* at 22 (observing that USDA must comply with NEPA when regulating biotechnology products).

[104] *See* GENE DRIVES, *supra* note 32, at 114.

[105] *Id.* at 112.

[106] *See id.* at 115.

[107] *See* EA, *supra* note 2, at 115, 118-21 (concluding that ecosystem effects, as well as toxic or allergenic effects on animals or humans, will be negligible); *see also id.* at 73-97 (evaluating potential impacts). As the NAS report suggests, the Oxitec EA has "some relevance to gene drives" because it involves a genetically engineered mosquito. GENE DRIVES, *supra* note 32, at 114-15.

[108] *See* GENE DRIVES, *supra* note 32, at 115, 158 (noting that NEPA does not require these things).

[109] For a case study suggesting how such an assessment might be carried out, see GENE DRIVES, *supra* note 32, at 123-26. *See also* European Food Safety Authority,

Oxitec's characterization of its proposed release as investigational further constricted the scope of FDA's NEPA analysis. By focusing on the effects of the "short term field trial as proposed,"[110] FDA was able to dismiss a number of concerns. For example, the agency concluded that populations of other mosquito species would not increase because the *A. aegypti* population "would be expected to recover to pre-trial numbers after the cessation of . . . releases."[111] Similarly, the agency found a "low" probability that a transgenic female mosquito would bite a human, based on the numbers of mosquitoes to be released during the trial and the limited human population in the trial area.[112]

That FDA narrowly focused its environmental impact analysis on this one field trial is not surprising. Oxitec sought permission to proceed only with this one trial, and the effects of a broader release are especially uncertain. Rather than assessing the implications of a broader release, the agency's discussion of cumulative impacts focused on the effects of Oxitec's field trial "coupled with the continued use of insecticides and other vector control methods," and declared that "[c]onsideration of any future field trials at this time would be purely speculative."[113] The scope of FDA's analysis is consistent with NEPA case law, which generally does not require agencies to consider the broader programmatic implications of an individual experiment unless the experiment is part of a defined program.[114] Nonetheless, NEPA analysis is supposed to consider the effects of connected, cumulative, and similar actions.[115] Because Oxitec's field trial is arguably connected to further field trials and represents a critical step toward the commercial release of the mosquito on a far greater scale, further analysis would have been appropriate.

*Guidance on the Environmental Risk Assessment of Genetically Modified Animals*, EFSA J., 2013, at 73-111 (discussing environmental risk assessment steps for genetically modified insects).

[110] FONSI, *supra* note 77, at 5.

[111] EA, *supra* note 2, at 102.

[112] *Id.* at 100.

[113] FONSI, *supra* note 77, at 7-8.

[114] *See, e.g.*, Found. on Econ. Trends v. Lyng, 817 F.2d 882, 884-85 (D.C. Cir. 1987) (no programmatic EIS required for "diverse and discrete" animal productivity research projects); Found. on Econ. Trends v. Heckler, 756 F.2d 143, 146 (D.C. Cir. 1985) (vacating lower court injunction against GMO deliberate-release experiments in absence of a programmatic EIS).

[115] 40 C.F.R. § 1508.25 (2017).

### *B. Uncertainty*

The Framework falls short not only in analyzing risk, but also in identifying and responding to uncertainty.[116] Attending to uncertainty can lay the foundation for research, facilitate planning for potential consequences, and enhance the credibility and transparency of decision making processes.[117] The Framework does acknowledge that agencies may lack sufficient information to determine whether a genetically modified organism poses unreasonable risks.[118] However, the Framework does little to address the issue, other than to observe that "agencies may need to collect information" in such instances.[119]

For new technologies, society often possesses far less information than necessary for sound decision making, and residual uncertainty looms large. As a general matter, federal agencies have been instructed to acknowledge the uncertainty associated with emerging technologies.[120] Instead of grappling with the problem of uncertainty, however, the Framework gives agencies an overarching directive to exercise oversight "only where the risk posed by the introduction [of a genetically engineered organism] is unreasonable."[121] Consistent with this directive, the 2017 update declares that regulation should follow a "risk-based approach" and that "[e]xercise of agency oversight . . . should be commensurate with the risk posed."[122] This approach essentially instructs agencies to balance risks against the costs of reducing such risks and to disregard the uncertainty that accompanies new biotechnologies.[123]

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[116] I use the term uncertainty here to refer to both epistemic uncertainty as well as the "unknown unknowns" sometimes characterized as ignorance. *See* NAT'L RES. COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT 97 (2009) [hereinafter SCIENCE AND DECISIONS] (defining uncertainty as "lack of information, incomplete information, or incorrect information"); NAT'L RES. COUNCIL, UNDERSTANDING RISK: INFORMING DECISIONS IN A DEMOCRATIC SOCIETY 106-07 (Paul C. Stern & Harvey V. Fineberg, eds., 1996) [hereinafter UNDERSTANDING RISK] (discussing various forms of uncertainty).

[117] *See* SCIENCE AND DECISIONS, *supra* note 116, at 98.

[118] 1992 Update, *supra* note 50, at 6757.

[119] *Id.*

[120] *See, e.g.*, Memorandum from John P. Holdren et al. for the Heads of Executive Departments and Agencies 3 (Mar. 11, 2011), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/etipc-memo-3-11-2011.pdf (encouraging agencies generally to ensure that benefits of regulation justify the costs "to the extent permitted by law" and recognizing the relevance of uncertainty and the limits of quantification and monetary equivalents).

[121] 1992 Update, *supra* note 50.

[122] 2017 UPDATE, *supra* note 55, at 8.

[123] *See* 1992 Update, *supra* note 50.

When the uncertainty associated with a decision is low, such an approach may be sensible.[124] But high levels of uncertainty — as is likely to be the case for gene-drive modified organisms and other new biotechnologies[125] — warrant greater attention to uncertainty analysis. Such analysis can qualitatively describe or quantitatively estimate uncertainties. Through uncertainty analysis, experts can specify ranges of estimates, identify key assumptions, and conduct sensitivity analyses.[126] Furthermore, uncertainty may justify adoption of one of various possible precautionary approaches to risk management. Regulators might choose whichever option avoids the least acceptable outcome.[127] Such an approach need not lead to rejection of a new technology; for example, significant risk of a Zika outbreak might warrant release of Oxitec's mosquitoes even if all hazards cannot be fully analyzed.[128] Alternatively, regulators might weigh the best and worst potential outcomes in deciding what to do.[129] At the least, decision makers should account for sources of uncertainty that are identified in risk assessments.[130]

The Oxitec EA illustrates the scant attention often given to uncertainty. The 124-page document makes no explicit mention of uncertainty outside of a brief discussion toward the end of the document titled "Uncertainties in the risk assessment."[131] In that one-page discussion, the EA makes the generic statement that uncertainty "can come from a variety of sources, such as variability in parameters

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[124] *Cf.* Daniel A. Farber, *Uncertainty*, 99 GEO. L.J. 901, 905 (2011) (suggesting that "conventional risk assessment is adequate without any special need for precaution . . . when the probability of harm can be reasonably ascertained").

[125] *See* GENE DRIVES, *supra* note 32, at 150.

[126] *See* NAT'L RES. COUNCIL, SCIENCE AND JUDGMENT IN RISK ASSESSMENT 160-87 (1994); UNDERSTANDING RISK, *supra* note 116, at 106-16 (discussing uncertainty analysis in the context of risk characterization).

[127] Deryck Beyleveld & Roger Brownsword, *Emerging Technologies, Extreme Uncertainty, and the Principle of Rational Precautionary Reasoning*, 4 LAW, INNOVATION, & TECH. 35, 45, 47 (2012); *see* Cass R. Sunstein, *The Catastrophic Harm Precautionary Principle*, 6 ISSUES IN LEGAL SCHOLARSHIP: CATASTROPHIC RISKS: PREVENTION, COMPENSATION, AND RECOVERY 1, 28 (2007).

[128] *Cf.* Nathanael Johnson, *Americans Love Genetically Modified Mosquitoes Much More than Other GMOs*, GRIST (Aug. 27, 2016), http://grist.org/article/americans-love-genetically-modified-mosquitoes-much-more-than-other-gmos (suggesting that public support for release of genetically modified mosquitoes is proportional to intuitions about personal risks, including risk of Zika infection).

[129] *See* Farber, *supra* note 124, at 930-31, 958.

[130] GENE DRIVES, *supra* note 32, at 150.

[131] EA, *supra* note 2, at 121-22.

and the limitations of their understanding."[132] The remainder of the discussion offers no analysis of uncertainty surrounding a specific issue other than to note that "[s]ome uncertainty exists for the occurrence of adverse weather conditions being encountered during the course of the trial and preventing rearing or release."[133] "[R]elying on . . . judgment by professionals . . . to estimate the degree of uncertainty," the EA concludes with "a high degree of certainty" that Oxitec's transgenic mosquitoes would have limited dispersal and are unlikely to become established in the environment.[134]

Because Oxitec's mosquitoes have been the subject of several field trials in other countries, the planned Florida release involves less uncertainty than would a first-time release. Nonetheless, the brief treatment of uncertainty in the EA offers little sense of whether worst-case scenarios are plausible or how much uncertainty is associated with the analyzed risks. If future application of the Coordinated Framework to decisions addressing gene drive modified organisms produces similarly sparse evaluations of uncertainty, such evaluations should be deemed inadequate.

### C. *Consent and Public Engagement*

The Framework leaves issues of consent and public engagement largely unaddressed. Its most detailed treatment of these issues, found in case studies prepared for the 2017 Update, briefly identifies public notification and comment requirements within the regulatory process.[135] Tellingly, in each of these case studies, FDA provides far less opportunity for public engagement than the other Framework agencies; EPA and USDA offer multiple opportunities for public comment, whereas FDA merely "posts the results of the completed consultation on its website."[136]

As the Oxitec case study illustrates, GMO policy decisions and public engagement are not confined to the federal level. FDA's FONSI determination, which was preceded by a voluntary public comment process, signaled federal consent. Much of the decision-making process occurred at the local level, however. Local authorities initiated the process of deploying the genetically modified mosquitoes, held a nonbinding referendum, and ultimately must approve contracts for

[132] *Id.* at 121.
[133] *Id.*
[134] *Id.* at 121-22.
[135] *See, e.g.*, 2017 UPDATE, *supra* note 55, at 41-42.
[136] *See id.*

Oxitec's services. Depending on the exact location of release, GMOs could move beyond local boundaries, suggesting that neighboring jurisdictions, state regulators, or foreign governments also could have interests that merit protection. Furthermore, the experimental nature of Oxitec's release and the potential effects on residents raise questions regarding whether the informed consent of individuals is necessary.

Informed consent is "a process intended to ensure that human subjects who will be observed or involved in a research activity are fully and explicitly advised of all risks, costs or inconveniences they may bear as a result of participating as a research subject, and voluntarily agree to accept or bear those risks and costs."[137] The ethical requirement of informed consent applies to human research subjects — i.e., "individuals who are the subjects of specific interventions or interactions, or from whom identifiable information, specimens or materials are collected."[138] Research involving human subjects is typically subject to review by an institutional review board or similar institution charged with considering ethical issues and ensuring informed consent.[139] Health and safety monitoring also may be necessary for studies that expose research subjects to significant risks.[140]

Does Oxitec's field trial require informed consent? Oxitec's inquiry focuses on mosquito populations: its stated objective is to study the expression of its genetic modification in wild mosquito populations and any reduction in those populations.[141] Indeed, because neither dengue nor Zika is present in the Florida Keys at significant levels, Oxitec cannot currently study whether its genetic modification would effectively combat these diseases in the Florida Keys.[142] Although humans will be present in any test location and subject to the risk of being bitten by a genetically modified mosquito, the standard

[137] WHO, *supra* note 39, at 78.

[138] *Id.* at 72, 78.

[139] *See* Resnik, *supra* note 42, at 43.

[140] *See id.*

[141] *See* EA, *supra* note 2, at 16.

[142] *Cf.* WHO, *supra* note 39, at 16 (distinguishing between entomological and epidemiological endpoints in measuring the efficacy of genetically modified mosquitoes); Resnik, *supra* note 42, at 42 (suggesting that the absence of dengue in the Florida Keys arguably makes its selection as a study site inappropriate). The local mosquito control district first expressed interest in Oxitec's mosquito after a local dengue outbreak, though the disease has not recurred in the Florida Keys. *See Science of Zika: The DNA of an Epidemic: Hearing Before the Comm. on Sci., Space, & Tech.*, 114th Cong. 59-61 (2016) (statement of Haydn Parry, Chief Executive Officer, Oxitec).

definition of human research subjects arguably does not encompass such persons. Elaborating on this view, a World Health Organization report concluded that "simply living in the vicinity of a [genetically modified mosquito] release is not sufficient grounds to require informed consent" in the absence of direct interventions upon individuals or collection of data from individuals.[143] However, the fact that Oxitec's research focuses on mosquito populations, and not humans, does not render irrelevant the notion of informed consent. Interests of individual autonomy argue in favor of obtaining informed consent if the magnitude and probability of potential hazards are sufficiently large.[144]

What procedures might informed consent require for Oxitec's field trial? The impracticality of obtaining consent from each potentially affected individual has led some to suggest community authorization as an alternative mechanism for protecting individuals' interests.[145] Community authorization, like informed consent, ideally involves public engagement, a deliberative process, a meaningful opportunity for affected persons to voice their concerns, and a degree of responsiveness to those concerns.[146] Unlike individualized consent, community authorization involves some form of group decision making.[147] Short of actual individual or community consent, other mechanisms could be adopted to protect local residents' interests. For example, if genetically modified mosquitoes could lead to increased risk of disease, research sponsors could make resources available for testing and treatment.[148] In addition, researchers could provide advance notice of releases, distribute insect spray to persons objecting to a study, and use other tools to minimize exposure.[149]

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[143] WHO, *supra* note 39, at 79; *see also United States*, *supra* note 11 ("Informed consent is a process for getting permission before conducting a healthcare intervention on a person. Our approach is emphatically not a healthcare intervention and we make no healthcare claims.").

[144] *Cf.* James V. Lavery et al., *Ethical, Social, and Cultural Considerations for Site Selection for Research with Genetically Modified Mosquitoes*, 79 AM. J. TROPICAL MED. & HYGIENE 312, 314, 316 (2008) (stating that "it is less clear when [environmental release] trials actually become human subjects research" but suggesting that "[t]he presumption should always be that informed consent will be sought from identifiable individuals who are likely to be exposed to research-related risks").

[145] WHO, *supra* note 39, at 79; *see also* Resnik, *supra* note 42, at 44-45 (noting the difficulty of obtaining consent from all individuals exposed to risk and discussing the conflict between individual rights and community good).

[146] *See* WHO, *supra* note 39, at 79-80.

[147] *Id.* at 80.

[148] Resnik, *supra* note 42, at 45.

[149] *See* Darryl Macer, *Ethical, Legal and Social Issues of Genetically Modifying Insect*

Even if limited field trials do not mandate informed consent, public engagement is widely viewed as essential in the course of introducing new technologies.[150] Public engagement can contribute to democratic governance and procedural justice, foster mutual learning and substantively better outcomes, and facilitate acceptance of new technologies.[151] In the Florida Keys, public engagement efforts (aside from the referendums) included town hall meetings, radio interviews, and door-to-door campaigns.[152] These efforts resemble Oxitec's outreach efforts in other countries. In Malaysia, for example, Oxitec distributed information about its planned trial to local communities and sought local approval, and the Malaysian government published announcements in national newspapers and sought input through a government website.[153] In Brazil, methods of information dissemination have included "local media (radio, TV, and press), community meetings, printed information (posters and leaflets), school presentations, carnival parades, use of small vans with loudspeakers and social media (websites and blogs)."[154]

*Vectors for Public Health*, 35 INSECT BIOCHEMISTRY & MOLECULAR BIOLOGY 649, 653-54 (2005).

150 Lavery et al., *supra* note 144, at 316.

151 *See* ALBERT C. LIN, PROMETHEUS REIMAGINED: TECHNOLOGY, ENVIRONMENT, AND LAW IN THE TWENTY-FIRST CENTURY 19-23 (2013); GENE DRIVES, *supra* note 32, at 133-35.

152 *On the Ground in Florida with Oxitec's Derric Nimmo: Part 2*, OXITEC (Sept. 23, 2016), http://www.oxitec.com/ground-florida-oxitecs-derric-nimmo-part-2.

153 T.S. Saraswathy Subramaniam et al., *Genetically Modified Mosquito: The Malaysian Public Engagement Experience*, 7 BIOTECHNOLOGY J. 1323, 1325 (2012). Environmental nongovernmental organizations ("NGOs") were specifically invited to comment, and a government advisory committee incorporated input from NGO scientists. *See id.* However, as was the case in the United States, neither Oxitec's permit application nor much of the data supporting the Malaysian government's risk analysis was made publicly available. *See* R. Guy Reeves et al., *Scientific Standards and the Regulation of Genetically Modified Insects*, PLOS NEGLECTED TROPICAL DISEASES, Jan. 2012, at 1, 8-9, http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0001502&type=printable.

154 Danilo O. Carvalho et al., *Suppression of a Field Population of* Aedes aegypti *in Brazil by Sustained Release of Transgenic Male Mosquitoes*, PLOS NEGLECTED TROPICAL DISEASES, July 2, 2015, at 1, 4, http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0003864&type=printable; *see* Margareth Lara Capurro et al., *Description of Social Aspects Surrounding Release of Transgenic Mosquitoes in Brazil*, 7 INT'L J. RECENT SCI. RES. 10363, 10364, 10366-67 (2016). Outreach efforts also included a door-to-door campaign in which a project "instructor" visited every home in the release area to inform residents about the planned releases. *Id.* at 10367. The door-to-door efforts were particularly effective at generating widespread awareness of the releases, but admittedly would be impractical on a larger scale. *See id.* at 10367-68.

These outreach efforts have achieved some success in informing residents,[155] but ultimately do not reflect the deliberation and give-and-take of genuine public engagement.[156] Public engagement involves more than information dissemination. Admittedly, in-depth public engagement can be difficult to undertake, and determining the goals, participants, and specific mechanisms of engagement may not be a straightforward task.[157] Nonetheless, public engagement should be an ongoing process that incorporates "communication, deliberation, relationship building, reflection, and empowerment."[158] This process can incorporate consensus conferences, citizen juries, or other similar tools that promote deeper understanding and deliberation.[159] In the context of a genetically modified mosquito field trial, project organizers might seek input regarding how a project should be designed or whether a release should occur at all.

Regardless of the specific tools used, the engagement process should be transparent. Both public engagement and informed consent require the sharing of information that can be understood, assessed, and verified.[160] FDA's reliance on its new animal drug authority to govern Oxitec's mosquito, however, has contributed to a perceived lack of transparency.[161] Recognizing that new drug applications often contain proprietary information, FDA treats such applications as confidential.[162] Confidential treatment protects the business interests of applicants, but undermines regulators' efforts to build public confidence in emerging technologies.[163] The NAD application process itself provides for little public input,[164] although FDA compliance with

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[155] One study found that outreach efforts and media coverage in the Florida Keys raised public awareness of the proposed field trial, but large segments of the community remained unaware or opposed. *See* Kacey C. Ernst et al., *Awareness and Support of Release of Genetically Modified "Sterile" Mosquitoes, Key West, Florida, USA*, 21 EMERGING INFECTIOUS DISEASES 320, 320 (2015); *see also* HOLLY RHODES & KEEGAN SAWYER, PUBLIC ENGAGEMENT ON GENETICALLY MODIFIED ORGANISMS 17 (2015).

[156] *See* GENE DRIVES, *supra* note 32, at 138; RHODES & SAWYER, *supra* note 155.

[157] *See* GENE DRIVES, *supra* note 32, at 136-39.

[158] *Id.* at 131.

[159] *See* LIN, *supra* note 151, at 36-37; GENE DRIVES, *supra* note 32, at 138.

[160] *See* Reeves et al., *supra* note 153, at 10.

[161] *See* RHODES & SAWYER, *supra* note 155, at 35 (noting public concerns regarding "lack of communication from federal agencies conducting environmental risk assessments of a potential release"); *see also* FOE, *supra* note 25, at 4 (noting lack of public consultation and FDA failure to hold public meetings with respect to Oxitec's proposal).

[162] *See* 21 C.F.R. §§ 514.11-.12 (2017).

[163] *See* Reeves et al., *supra* note 153, at 10.

[164] *See FDA's Response to Public Comments on Draft Guidance for Industry #187, Released*

NEPA does allow the agency to solicit public comment before an NAD is approved.[165] However, NEPA compliance offers a limited forum for the discussion of environmental impacts or social concerns because it occurs relatively late in the drug development and approval process.

## CONCLUSION

The regulatory response to Oxitec's proposed field trial illustrates the continuing inadequacy of the Coordinated Framework for managing biotechnologies. More generally, the recent update to the Framework represents a missed opportunity to address regulatory gaps and recognize the technological changes of the last three decades. A better approach would empower regulatory agencies having relevant expertise to exercise oversight, openly acknowledge uncertainties, and engage the public in deeper and more meaningful ways. However, the Trump administration hardly has expressed interest in biotechnology policy to date, and its deregulatory bent suggests little likelihood of strengthening the Framework.[166] Nonetheless, forthcoming efforts to introduce genetically modified mosquitoes, as well as other bioengineered organisms, will present opportunities to encourage advances in biotechnology while managing risks and addressing public concerns.

*9/18/2008*, FDA, http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm113612.htm (last updated May 2, 2017).

165 *See* 2017 GUIDANCE 187, *supra* note 59, at 9, 14.

166 *See* Brooke Borel, *The U.S. Regulations for Biotechnology Are Woefully out of Date*, SLATE (Apr. 21, 2017, 7:08 AM), http://www.slate.com/articles/technology/future_tense/2017/04/u_s_biotechnology_regulations_are_woefully_out_of_date.html (noting that "the new administration doesn't seem to be paying much attention" to biotechnology policy).