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Dr. Bernadette Dunham
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Food and Drug Administration
7519 Standish Place, HFV-12
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February 12, 2015

Dear Dr. Dunham:

We write this letter to urge the Food and Drug Administration ("FDA") to halt Oxitec's unregulated release of millions of genetically engineered *Aedes aegypti* mosquitos (hereinafter, the "Oxitec mosquito") in Key Haven, Florida this spring.

The attached *Associated Press* article indicates that the FDA is "thoroughly evaluating all necessary information" and suggests that the agency is considering whether or not to approve the release. We are pleased by the notion that the agency would take an active role in regulating the Oxitec mosquito, ostensibly in order to prevent it from causing any harm to human health and the environment. But, as detailed in the remainder of this letter, to the extent that the agency has the authority to regulate the mosquito, it must require Oxitec to submit a New Animal Drug Application ("NADA"). The Food, Drug, and Cosmetic Act ("FDCA") bars the agency from expressly or tacitly allowing the release in any other way. Therefore, we urge the agency to stop the uncontrolled release of Oxitec mosquitos by requiring that the company submit a NADA for formal agency review.

As you are aware, an agency's authority is limited to the terms of its organic statute or those powers necessarily implied by such terms.[1] FDA's Guidance for Industry 187 indicates that that the agency derives its powers to regulate genetically engineered animals under the new animal drug provisions of the FDCA.[2]

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[1] *See La. Public Serv. Com v. FCC,* 476 U.S. 355, 374 (1986) (*"*an agency literally has no power to act, . . . unless and until Congress confers power upon it[;]) *Arrow-Hart & Hegeman Electric Co. v. FTC*, 291 U.S. 587, 598 (1934) ("an administrative body possess[es] only such powers as are granted by statute[;]") *United States v. Miami Univ.*, 294 F.3d 797, 807 (6th Cir. 2002) ("If Congress does not expressly grant or necessarily imply a particular power for an agency, then that power does not exist." (citing *Walker v. Luther*, 830 F.2d 1208, 1211 (2d Cir. 1987)).

[2] *See* Guidance for Industry 187, Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs Final Guidance, U.S. Department of Health and Human Services, Food and Drug Administration Center for Veterinary Medicine at 5-6 (January 15, 2009) ("Guidance 187"):

> FDA's authority over new animal drugs comes from the [FDCA] (21 U.S.C. 321 et seq.) The definition of a drug, in section 201(g) of the Act, includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The definition of "new animal drug" in section 201(v) of the Act includes that it is a drug intended for use in animals that is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling, and that has not been used to a material extent or for a material time. . . . The rDNA construct in a GE animal

Under these provisions, a new animal drug "*shall*, with respect to any particular use or intended use of such drug, be deemed unsafe" and thus adulterated,[3] unless (among other reasons not relevant here), it 1) conforms to an FDA-approved NADA in effect for that particular use,[4] 2) is a conditional approval or index listing for such drug,[5] or 3) it is for investigational use and conforms to the terms of an existing exemption regulation.[6]

It is unclear how the FDA intends to exercise its regulatory authority to evaluate the Oxitec mosquito. But, as the agency's Guidance 187 acknowledges, conditional approval and indexing are not permitted for genetically engineered organisms.[7] Further, it is our understanding that FDA has opened an Investigational New Animal Drug ("INAD") file for the mosquito, indicating that the agency has begun to regulate the animal as such, pursuant to its existing investigational-use exemption regulations and Guidance 187.

But none of FDA's INAD regulatory exemptions allow for such approval, as they only apply to new animal drugs for *in vitro* and laboratory research animals and clinical examinations.[8] Given that Oxitec is planning to release thousands of its animals treated with the genetic construct into the wild for its experiment, the animal drugs does not qualify as an INAD.

Therefore, to the extent that the agency has any authority to regulate the Oxitec mosquito as a new animal drug, it must do so under the agency's NADA process. Moreover, while the agency's Guidance 187 indicates that in certain cases it may exercise its enforcement discretion, such as it did after reviewing information about *Zebra danio* aquarium fish ("GloFish"), the agency does not have same amount of discretion in the present matter. There, the FDA's response to the manufacturing company's informal inquiry—issued prior to its issuance of its Guidance 187—was simply not to take any enforcement action against the GloFish at that time.[9] In the present matter, however, the agency has apparently opened an INAD file, which, pursuant to Guidance 187, is "established containing information on investigational GE animals," and is done after the agency has determined that the GE construct is subject to the agency's new animal drug authority. Accordingly, since FDA has begun to regulate the mosquito as a new animal drug, it cannot refuse to continue or complete such regulatory action under the guise of exercising enforcement discretion.[10]

Moreover, since the FDA's review of *Zebra danio* aquarium fish matter, the agency's guidance has spelled out precisely how the agency will exercise its enforcement discretion under the FDCA, stating that among the factors it intends to consider are:

> 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, meets the [FDCA] drug definition.

[3] 21 U.S.C. § 360b(a)(1) (2012) (emphasis added.)
[4] *Id.* § 360b(a)(1)(A).
[5] *Id.* § 360b(a)(1)(B)-(C).
[6] *Id.* § 360b(a)(3).
[7] 21 U.S.C. §§ 360ccc-1(a)(2), 360ccc(a)(3)(A) (2012).
[8] 21 C.F.R. § 511.1(a)-(b) (2014).
[9] As one court put it "[t]here is no indication that the defendants are affirmatively endorsing GloFish as 'safe' under the FDCA . . . ." *International Center for Technology Assessment v. Thompson*, No. 04-0062, slip op. at 21 (Doc. 4) (D.D.C. Mar 30, 2005).
[10] *Allergan, Inc. v. Shalala*, 1994 U.S. Dist. LEXIS 21716 (D.D.C. Nov. 10, 1994)

• Whether there is anything about the article itself that poses a human, animal, or environmental risk. For example, does the construct contain sequences that can cause human or animal disease either intrinsically or by recombination?

• Whether, in the event of an environmental release, the GE animal poses any more of an environmental risk than its non-GE counterpart.

• Whether there are concerns over the disposition of GE animals that could pose human, animal, or environmental risks e.g., would disposal of large numbers of dead GE ferrets containing a construct that makes them resistant to rabies pose a particular risk?

• Whether there are any other safety questions that have not been adequately addressed by the sponsor.[11]

Given that the agency has now stated that it will evaluate both the human and animal health risks of genetically engineered animals such as the Oxitec mosquito, including whether safety questions have been adequately addressed by the sponsor, the agency is not free to refuse to regulate a GE animal if doing so amounts to an approval of a New Animal Drug under a less stringent standard than required by the FDCA.[12] After all, the act *requires* that the agency reject a NADA if it has, among other reasons, "insufficient information to determine whether such drug is safe for use under such conditions."[13] Thus, for FDA not to halt the release of the Oxitec mosquitos—at least to subject the genetically engineered organism to review as a new animal drug—on the grounds that the agency has insufficient information on the animal's safety would be to violate Congress's clear instructions that new animal drugs are to be presumed unsafe unless they are approved by the agency through the NADA process.[14]

While such a safety determination is usually made after a drug sponsor has submitted a NADA or FDA has made an decision to enforce the act, it is illegal for a new animal drug sponsor to not submit a NADA when the drug does not fit within one of its exemption provisions, and FDA cannot be complicit in this unlawful behavior.[15] Moreover, the agency cannot preclude enforcement by abdicating its own statutory responsibilities.[16]

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[11] Guidance 187 at 8.

[12] *See Util. Air Regulatory Group v. EPA*, 134 S. Ct. 2427, 2445 (2014) (stating that it is not a proper use of enforcement discretion for an agency to alter permitting requirements and to establish that otherwise-prohibited conduct will not violate the law).

[13] 21 U.S.C. § 360b(d)(1)(D); 21 C.F.R. § 514.111(a)(4) (2014). *See also Delta Air Lines, Inc. v. Export-Import Bank of the United States*, 718 F.3d 974, 977 (D.C. Cir. 2013) ("Ensuring that agencies follow commands of this sort is of course standard judicial fare.") (citing Richard J. Pierce, Jr. Administrative Law Treatise § 17.6 (4th ed. 2002)) ("'statute can confer on an agency a high degree of discretion, and yet a court might still have an obligation to review the agency's exercise of its discretion to avoid abuse,' especially on procedural grounds")).

[13] 21 U.S.C. § 360b(d)(1)(D). *See also* 21 C.F.R. § 514.111(a)(4).

[14] *See* 21 U.S.C.. § 360b(a)(1).

[15] *Cf. Schering Corp. v. Heckler*, 779 F.2d 683, 685-86 (D.C. Cir. 1985) (distinguishing FDA's discretion in postponing a decision to enforce the FDCA's new drug provisions to determine whether the drug is subject to the act's provisions and deeming the substance a new animal drug that is safe and effective); *accord Int'l Union, UAW v. Brock*, 783 F.2d 237, 246 (D.C. Cir. 1986) (interpreting the

Nor may the agency disregard its guidance in reviewing the release of the Oxitec mosquito.[17] The sparse information that is publicly available about the organism indicates that it poses a serious risk to the environment and public health. For example, a published scientific review indicates that Oxitec has failed to conduct, no less publish, any study showing that the tetracycline controlled transcriptional activation (tTA) gene, which is the gene construct that eventually kills the mosquito, is not expressed in the salivary gland and therefore cannot be passed on to humans.[18] Therefore, "there is the plausible concern that females could inject tTA into humans along with mosquito salivary gland fluids that are transferred as part of a normal bite."[19] Even though we understand that officials only plan to release non-biting male mosquitos, up to 0.5 percent of the released mosquitos in fact could be female.[20]

Further, the tTA protein seems to be either ineffective in some mosquitos or prone to resistance.[21] Oxitec's own study reveals that as many as 15 percent of the mosquitos survived for some time after inadvertent exposure to low levels of tetracycline in a laboratory.[22]

Bites from genetically engineered female mosquitos could cause allergies or irritation in humans, and diseases transmitted by mosquitos could evolve to become more dangerous due to the genetic engineering. Other unexamined and potentially harmful effects include those from a population boom of resistant, tetracycline-exposed, or otherwise surviving breeding mosquitoes that can bite and spread dengue virus or other diseases. Ingestion of these insects and their

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Schering decision as applying to an agency decision that "could not be characterized as a decision affecting the underlying legal or factual issues").

[16] *See Whitaker v. Clementon Housing Authority*, 788 F. Supp. 226, 231 (D.N.J. 1992) (citing *Heckler v. Chaney*, 470 U.S. 821, 833 n.4 (1985); *see also Public Citizen Health Research Group v. Commissioner, Food & Drug Admin.,* 740 F.2d 21, 32 (D.C. Cir. 1984) ("When agency recalcitrance is in the face of a clear statutory duty or is of such magnitude that it amounts to an abdication of statutory responsibility, the court has the power to order the agency to act to carry out its substantive statutory mandates." (citing *Adams v. Richardson*, 480 F.2d 1159 (D.C. Cir. 1973) (en banc) (per curiam); *Environmental Defense Fund, Inc. v. Ruckelshaus*, 439 F.2d 584, 594-595 (D.C. Cir. 1971))).

[17] *See* 21 U.S.C. § 371(h)(1)(B) ("Although guidance documents shall not be binding on the Secretary, the Secretary *shall* ensure that employees of the Food and Drug Administration do not deviate from such guidances without appropriate justification and supervisory concurrence.") (emphasis added). *Accord Sierra Club North Star Chapter v. LaHood***,** 693 F. Supp. 2d 958, 974 (D. Minn. 2010) **(**"The Supreme Court has "'frequently reiterated that an agency must cogently explain why it has exercised its discretion in a given manner.'") (quoting *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 48 (1983) and citing *F.C.C. v. Fox Television Stations, Inc.*, 129 S. Ct. 1800, 1811 (2009)). *See also Mickeviciute v. INS*, 327 F.3d 1159, 1162 (10th Cir. 2003) (stating that an agency abuses its discretion when its decision "inexplicably departs from established policies, is devoid of any reasoning, or contains only summary or conclusory statements.") (internal quotation marks omitted); *Zhao v. United States DOJ*, 265 F.3d 83, 93 (2d Cir. 2001)).

[18] Reeves RG, Denton JA, Santucci F, Bryk J, Reed FA (2012) Scientific Standards and the Regulation of Genetically Modified Insects. PLoS Negl Trop Dis 6(1) at 9: e1502. doi:10.1371/journal.pntd.0001502.

[19] *Id.*

[20] Andrew Pollack, "Concerns Are Raised About Genetically Engineered Mosquitoes," *New York Times*, Oct. 30, 2011.

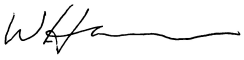
[21] *Id.*

[22] Sean Poulter, "Human health and the environment 'may be put at risk by genetically modified mosquitoes,'" *Globe and Mail*, Jan. 12, 2012.

manipulated DNA by non-target organisms could have unexpected health and environmental effects. Also, the ability to grow in the presence of tetracycline could unintentionally lead to Oxitec's mosquitos thriving in the wild. Despite the previous belief that *Aedes aegypti* only breed in clean water, recent studies indicate that these mosquitos can and do breed in septic tanks and raw sewage in the Florida Keys and elsewhere.[23] These locations are a source of possible tetracycline contamination and exposure could lead to high rates of survival for Oxitec's transgenic mosquitos. Additionally, disposing the large amounts of tetracycline used to raise GE mosquitos in the Keys will likely contaminate water sources and perpetuate the occurrence of antibiotic-resistant bacteria in the environment, leading to downstream human health impacts.

Given these issues, FDA's own guidance bars the agency from exercising any enforcement discretion and expressly or tacitly allowing the release of the Oxitec mosquito. And, because the agency has no authority to regulate the release of the mosquito as an INAD, the agency must require that the sponsor first obtain approval through the formal NADA process. We are happy to talk to you more about this matter. Please do not hesitate to call our Senior Staff Attorney, Zach Corrigan, at (202) 683-2451 if you have any questions.

Sincerely,



Wenonah Hauter
Executive Director

[23] Barrera R., Amador M., Diaz A., Smit J., Munoz-Jordan J.L. and Rosario Y. (2008). Unusual productivity of *Aedes aegypti* in septic tanks and its implications for dengue control. *Medical and Veterinary Entomology*, 22, 62-69; Beserra E.B., Fernandes C.R.M., Sousa J.T. de, Freitas E.M. and Santos K.D. (2010). Efeito da qualidade da água no ciclo de vida e na atração para oviposição de *Aedes aegypti* (L.) (Diptera: Culicidae). *Neotropical Entomology*, 39, 1016-1023, attached as Exhibit I; Burke R., Barrera R., Lewis M., Kluchinsky T. and Claborn D. (2010). Septic tanks as larval habitats for the mosquitoes *Aedes aegypti* and *Culex quinquefasciatus* in Playa-Playita, Puerto Rico. *Medical and Veterinary Entomology*, 24, 117-123, doi: 10.1111/j.1365-2915.2010.00864.x attached as Exhibit J; Hribar L., Vlach J., DeMay D., James S., Fahey J. and Fussell E. (2004). Mosquito larvae (Culicidae) and other Diptera associated with containers, storm drains, and sewage treatment plants in the Florida Keys, Monroe County, Florida. *Florida Entomologist*, 87, 199-203; Irving-Bell R.J., Okoli E.I., Diyelong D.Y., Lyimo E.O. and Onyia O.C. (1987). Septic tank mosquitoes: competition between species in central Nigeria. *Medical and Veterinary Entomology*, 1, 243-250; Martinez L. (2011). Aedes ya se reproduce en agua sucia. *La Prensa Gráfica*, 29 October.