CENTER FOR FOOD SAFETY

June 19, 2017

Docket No. FDA-2008-D-0394
The Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments on Draft Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals Docket No. FDA-2008-D-0394

To United States Food and Drug Administration (FDA):

Center for Food Safety (CFS) submits the following comments on behalf of itself and its members, as well as nonprofits the International Center for Technology Assessment and Foundation Earth, in response to FDA's Draft Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals.

CFS is a nonprofit, public interest advocacy organization dedicated to protecting food, farmers, and the environment. To implement this mission, CFS uses legal actions, groundbreaking scientific and policy reports, books and other educational materials, and grassroots campaigns, on behalf of its over 850,000 farmer and consumer members across the country. CFS is a recognized national leader on the issue of genetically engineered (GE) organisms, and has worked on improving their regulation and addressing their impacts continuously since the organization's inception.

Foundation Earth is a national nonprofit, public interest advocacy organization whose mission is to foster an earth-centered world view. Its focus includes economic models, technology, education, health, and the legal system.

The International Center for Technology Assessment (ICTA) is a nonprofit, nonpartisan organization committed to providing the public with full assessments and analyses of technological impacts on society. ICTA is devoted to fully exploring the economic, ethical, social, environmental, and political impacts that can result from the applications of technology or technological systems.

FDA does not have authority under its enabling statute to regulate GE animals or insects absent a GE-specific statute passed by Congress. FDA needs a GE-specific statute, with GE-specific regulations, that address the novel risks of GE animals. Efforts otherwise are ultra vires unlawful agency action. FDA cannot lawfully create a regulatory pathway for novel GE animals,

NATIONAL HEADQUARTERS
660 Pennsylvania Avenue, SE, Suite 302
Washington, D.C. 20003
T: 202-547-9359 F: 202-547-9429

CALIFORNIA OFFICE
303 Sacramento Street, 2nd Floor
San Francisco, CA 94111
T: 415-826-2770 F: 415-826-0507

PACIFIC NORTHWEST OFFICE
917 SW Oak Street, Suite 300
Portland, OR 97205
T: 971-271-7372 F: 971-271-7374

HAWAI'I OFFICE
1132 Bishop Street, Suite 2107
Honolulu, Hawaii 96813
T: 808-681-7688

office@centerforfoodsafety.org centerforfoodsafety.org

using a statute never so intended, through a "guidance" document. Such actions are procedurally and substantially unlawful, in addition to being in contravention of good governance principles.

I. FACTUAL BACKGROUND

Genetic engineering—specifically recombinant DNA (rDNA) technology—has existed for over forty years, but the question of how to regulate the technology has been misguided: an agency cannot extend jurisdiction over a novel technology by trying to fit it into an existing definition. In 2009, FDA first issued Guidance for Industry #187: "Regulation of Genetically Engineered Animals," in which it first explained its conclusion that it could extend its authority to cover GE animals because rDNA technology could fit within FDA's definition of a "drug" and "new animal drug," despite the fact that the Federal Food, Drug, and Cosmetic Act of 1939 (FFDCA), which grants FDA that authority, was never intended to regulate GE organisms.

The lack of a GE-specific statute from Congress has resulted in different agencies asserting jurisdiction over GE organisms without a coherent process or strategy for evaluating the health and environmental impacts such technologies impose. For example, in its guidance, FDA noted that it does not have jurisdiction to regulate GE animals if they otherwise meet the definition of a "plant pest" harm under the Plant Protection Act, and are regulated by USDA's Animal and Health Plant Inspection Service (APHIS).

Continuing with this approach to jurisdiction, FDA has reissued Guidance for Industry #187: as "Regulation of Intentionally Altered Genomic DNA in Animals." Under its revised guidance, FDA is changing the term "genetically engineered animals" to "intentionally altered genomic DNA in animals." Other changes FDA makes from prior versions of the guidance are less clear, since the agency does not fully clarify why or how it is revising its guidance.

All of the new kinds of biological engineering constitute what the industry, other nations, and the public call genetic engineering. This change of title, while perhaps intended to clarify the status of new kinds of genetic engineering, is misleading. The title should remain: "Regulation of Genetically Engineered Animals." The definition of genetic engineering can be updated, but the basic term of GE is still the most apt.

Furthermore, the Obama White House memorandum on the revisions of the coordinating framework makes clear that it intends agencies to include all genetic engineered products, not just those that are intergeneric. The key language is found in the first footnote to the White House memo:

> For the purpose of this memo, "biotechnology products" refers to products developed through genetic engineering or the targeted or in vitro manipulation of genetic information of organisms, including plants, animals, and microbes. It also

covers some of the products produced by such plants, animals, and microbes or their derived products as determined by existing statutes and regulations."[1]

A new definition of "genetic engineering" should start with the definition of genetic engineering being used by the National Academy of Sciences (NAS).[2]

> Genetic engineering means the introduction or change of DNA, RNA, or proteins by human manipulation to effect a change in an organism's genome or epigenome; where genome means the complete sequence of the DNA in an organism, and epigenome means the physical factors affecting the expression of genes without affecting the actual DNA sequence of the genome.
>
> Genetically engineered organism means an organism developed using genetic engineering; where organism is any active, infective, or dormant stage of life form of an entity characterized as living, including vertebrate and invertebrate animals, plants, bacteria, fungi, mycoplasmas, mycoplasma-like organisms, as well as entities such as viroids, viruses, or any entity characterized as living, related to the foregoing.

To the NAS definition, CFS recommends appending this revision of the FDA proposed definition:

This includes all animals whose genomes or epigenomes have been intentionally altered using modern molecular technologies, which may include random or targeted DNA sequence changes including nucleotide insertions, substitutions, or deletions, or other technologies that introduce specific changes to the genome of the animal. This definition applies to both the founder animal in which the initial alteration event occurred and the entire subsequent lineage of animals that contains the genomic/epigenomic alteration(s).

II. BACKGROUND

As an initial matter, neither FDA nor EPA has formal regulations specific to GE insects and animals. In 2002, the National Academy of Sciences published a report on GE animals stating that aquatic organisms and insects present the greatest environmental concerns because

[1] Memorandum for the Heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture (July 2, 2015), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf.

[2] NASEM, 2016. Genetically Engineered Crops: Experiences and Prospects. Washington, DC: National Academies Press, ISBN 978-0-309-43738-7 | DOI: 10.17226/23395, available at http://www.nap.edu/23395; NASEM, 2017. Preparing for Future Products of Biotechnology. Washington, DC: National Academies Press, ISBN 978-0-309-45205-2 | DOI: 10.17226/24605, available at http://www.nap.edu/24605; NASEM 2016 at 36 explicitly lists some examples of what its definition includes and excludes: "The committee's definition of genetic engineering includes recently developed technologies such as CRISPR, TALENs, and ZFNs [genome editing methods]." NASEM 2016. Glossary at 384 – 388; NASEM, 2017. Glossary at 178 – 180.

their mobility poses serious containment problems, and because they easily can become feral and compete with indigenous populations.[3] The report expressed concerns about gaps in regulation.

In the absence of a coherent regulatory framework on how to assess the risks of open releases of GE animals and insects in the U.S., it should be noted that the European Food Safety Authority (EFSA) has published guidance for environmental risk assessment under the European Union (EU)'s Deliberate Release Directive for genetically modified organisms (GMOs), although this does not yet cover the important area of food safety assessment. The EFSA guidance outlines the evidence that companies would need to provide for its GE insects to be placed on the EU market.[4] The EFSA guidance provides details on the following specific areas of risk for GE animals:

- Persistence and invasiveness of GE animals, including vertical gene transfer (VGT);
- Horizontal gene transfer;
- Pathogens, infections and diseases;
- Interactions of GE animals with target organisms;
- Interactions of GE animals with non-target organisms (NTOs);
- Environmental impacts of the specific techniques used for the management of GE animals; and
- Impacts of GE animals on human and animal health.[5]

In determining regulatory jurisdiction for GE animals and a framework that properly analyzes the environmental and human health impacts associated with such technologies, FDA, USDA, and EPA should all acknowledge and incorporate the EFSA Guidance.

III. DISCUSSION

A. FDA's Alleged Jurisdiction over GE Animals Is *Ultra Vires*.

This newest revised FDA guidance 187 continues the fiction of FDA's authority over GE animals under the FFDCA. FDA's attempted extension of its FFDCA authority to cover GE animals is *ultra vires*. Very simply, GE animals are entirely different than animal drugs. They create different risks, require different data, and have different definitions. Genetic engineering of an animal does not fit FDA's definition of a "new animal drug." The authority delegated from Congress to FDA in the FFDCA occurred long before genetic engineering even existed, and attempting to fit genetically engineered organisms into the "new animal drug" definition is attempting to fit square pegs in round holes.

---

[3] National Academy of Science, *Animal Biotechnology: Science Based Concerns* (2002), http://www.nap.edu/catalog/10418/animal-biotechnology-science-based-concerns.

[4] European Food Safety Authority (EFSA), *Guidance on the Environmental Risk Assessment of Genetically Modified Animals*, EFSA Journal 2013, 11(5):3200 (May 23, 2013), http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3200.pdf (hereinafter, EFSA Guidance).

[5] *Id.* at 73-107.

Ultra vires means "beyond the scope of power allowed or granted . . . by law."[6] An *ultra vires* action is premised on three basic tenets of administrative law.[7] First, "an agency's power is no greater than that delegated to it by Congress."[8] Second, agency actions beyond delegated authority are *ultra vires* and should be invalidated.[9] Third, courts look to an agency's enabling statute and subsequent legislation to determine whether the agency has acted within the bounds of its authority.[10]

The FFDCA does not authorize FDA to assert jurisdiction over the production and commercialization of GE animals or insects. The FFDCA defines "drugs" as (1) "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals"; and (2) "articles (other than food) intended to affect the structure or any function of the body of man or other animals."[11] The term "new animal drug" is defined as "any drug that is intended for use for animals other than man."[12] A GE animal is not a drug intended for use for animals other than man, and therefore does not fit the definition of a "new animal drug." Nonetheless, FDA asserted regulatory authority over GE animals in 2009 by issuing guidance that interpreted the definition of "new animal drug" to include GE animals, despite the fact that genetic engineering of animals and insects present enormously different risks and impacts than drugs, requiring different expertise, analyses, and regulation than were contemplated when Congress enacted the FFDCA.[13]

FDA should not be regulating any GE animals (including insects) under the FFDCA because it is an outdated statute never intended for that purpose. Since neither genetic engineered insects nor animals fit into the FFDCA's definition of a "new animal drug," FDA does not have jurisdiction over GE animals and insects. As a consequence, FDA's regulation of GE insects and animals under the FFDCA is inadequate and lacking in expertise, procedures, and data needed to protect health and the environment from the novel risks that genetically engineered organisms create. A new statute is required from Congress before the testing or approval of any GE animals or insects is considered. That statute should be specific to GE-technology, setting in place a pre-market, precautionary approval process, which addresses and analyzes the unique and novel health and environmental risks that GE organisms present.

B. FDA, EPA, and USDA Must Mandate GE-Specific Procedures.

---

[6] *Adamski v. Mchugh*, No. 14-cv-0094, 2015 WL 4624007, at *6 (D.D.C. Jul. 32, 2015) (citing Black's Law Dictionary 1755 (10th ed. 2014)).
[7] *Adirondack Medical Center v. Sebelius*, 29 F. Supp. 3d 25, 36 (D.D.C. 2014).
[8] *Id*. (citing *Lyng v. Payne*, 476 U.S. 926, 937 (1986)).
[9] *Id*. (citing *Transohio Say Bank v. Dir., Office of Thrift Supervision*, 967 F.2d 598, 621 (D.C. Cir. 1992)).
[10] *Id*. (citing *Univ. of D.C. Faculty Ass'n/NEA v. D.C. Fin. Responsibility & Mgmt. Assistance Auth.*, 163 F.3d 616, 620-21 (D.C. Cir. 1998)).
[11] 21 U.S.C. § 321(g)(1).
[12] *Id*. § 321(v)(1)-(2).
[13] FDA, Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs, at 3 (Jan. 15, 2009), available at https://web.archive.org/web/20090709170807/http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm113903.pdf (hereinafter, FDA Guidance or Guidance).

Until and unless there is new statutory authority, no GE animals or insects should be approved by any U.S. agency. Based on proper statutory authority, FDA, EPA, and USDA must improve their coordination in regulating GE organisms. Specifically, rather than haphazardly fitting regulation of GE organisms into existing statutory definitions to determine which agency has jurisdiction, FDA, EPA, and USDA should enact mandatory regulations that require specific procedures that each agency must utilize when analyzing the environmental and human health effects of GE organisms.

A cohesive interagency framework would help each agency employ their resources and expertise efficiently. For example, since FDA has authority to ensure the safety of drugs, and EPA has authority to ensure protection of the environment, it may be appropriate for FDA to evaluate the human health impacts of GE organisms, while EPA evaluates the environmental health impacts. The agencies should work together to draft regulations that set mandatory procedures for evaluating the safety and efficacy of GE organisms, such as requiring caged trials prior to all open releases. A coordinated framework would reduce the current uncertainty regarding jurisdiction over particular GE organisms and help establish a program that efficiently analyzes the health and safety impacts of releasing GE organisms.

C. Guidance 187 is an Improper Attempt at Rulemaking and Requires a Substantive Rulemaking and Programmatic Environmental Impact Statement.

Compounding its error in not having statutory authority, FDA has used a repeatedly revised guidance document to attempt to create a regulatory pathway for GE animals and now GE insects. This violates the APA. Mandatory, GE-specific regulations are needed to address the novel risks of GE animals. The repeated revisions, in effect, a moving target, show one of the many problems with creating an entire area of administrative practice through a guidance document. Guidance 187 is a disguised substantive rule that has granted GE animal manufacturers and engineers legal rights and has the force of law, and as such, it violates the APA and must be set aside.

In addition, Guidance 187 is a major federal action because it created and continues a new regulatory assessment pathway for GE animals under the FFDCA, opening the door to significant direct, indirect, and cumulative environmental impacts that are reasonably foreseeable. As such, Guidance 187 needs a programmatic environmental impact statement fully analyzing those impacts and is unlawfully issued without one.

D. In Binding Regulations, Under a Proper Statute, FDA Should Require a Full Environmental Impact Statement For Any GE Animal That Could Breed With Wild or Feral Relatives If It Escapes Confinement.

Many food animals have wild or feral relatives that they can breed with and produce offspring. Many GE animals, such as rainbow trout, can even breed with closely related other species. GE cattle could breed with the American Bison. Feral hogs, which could breed with GE hogs, are found in virtually every part of the US. Because of this high likelihood of GE animals interbreeding with their wild relatives, FDA should require an EIS for any GE animal

that could breed with wild or feral relatives or other related species routinely allowed to grow outside, such as cattle, sheep, or goats raised on grasslands and not confined. FDA should fully examine with competent researchers the potential for environmental impacts, including the potential for inadvertent release or escape of the genetically engineered animal and/or its products into the environment, and whether any biocontainment, geographical containment measures can mitigate any potential significant impacts that would adversely affect the natural, farming or human environment. Any GE animal that has a wild relative that is an endangered species should not be allowed to be developed until a determination has been made by the Fish and Wildlife Service or National Marine Fisheries Service through formal consultation that no risk to an endangered species would come from the potential escape of the GE animal or any other impacts from it.

E. Investigational Food Use Authorizations Do Not Constitute Adequate Food Safety Review.

Additionally and alternatively, if FDA continues to attempt to regulate GE animals under the FFDCA, FDA should require a two-tier review of all animals genetically engineered as food. It has required that the products animals genetically engineered to produce human drugs in their milk (a GE Goat) or their egg whites (GE chicken) be tested for their safety and efficacy by FDA drug reviewing authorities and the FDA New Animal Drug Review demonstrates the safety of the genetic construct for the GE animal. Similarly, the FDA should use the NADA review to demonstrate the safety of the genetic engineering for the GE animal, but then it should proceed to have the products from the GE animal tested as new food additives. This would allow testing of the food from GE animals to get tested in much the same way that drugs from GE animals are already being tested. The new food additive testing would require more rigorous tests of these new genetic engineered foods than the *ad hoc* food safety review used for the GE salmon. The Food Additive Review process standards are clear and would not have to be re-invented on a case by case basis.

F. FDA Should Require Complete Sequencing Of The Genomes of Genetically Engineered Animals.

Again, assuming FDA continues to attempt to regulate GE animals under the FFDCA, many new kinds of genetic engineering are touted as being more precise methods of genetic engineering that earlier methods, however, research[14] is demonstrating that these new techniques, such as CRISPR Ca9 have many "off target" effects. Simply put, these new techniques can result in "gene edits" to parts of the genome that are unintended. Requiring full genomic sequences, not just sequences of the area near the intended site of the genetic engineering must be required by the FDA. According to Dr. Steven Tsang, one of the co-authors of a recent study

[14] See for example: Wu, W.H. et al. CRISPR repair reveals causative mutation in a preclinical model of retinitis pigmentosa. Mol. Ther. 24, 1388–1394 (2016); Indiana University. "Insects resist genetic methods to control disease spread, study finds: Study challenges use of powerful gene-editing technology CRISPR-Cas9 to prevent malaria, other diseases." ScienceDaily. ScienceDaily, 19 May 2017, www.sciencedaily.com/releases/2017/05/170519151441.htm.

of CRISPR in mice, "Researchers who aren't using whole genome sequencing to find off-target effects may be missing potentially important mutations. Even a single nucleotide change can have a huge impact." [15]

G. EPA Should Regulate Genetically Engineered Insects.

In the absence of a GE-specific statute, EPA should regulate GE insects. EPA has experience regulating mosquitoes infected with Wolbaccia bacteria and has already supervised field trials of *Aedes albopictus* and *Aedes aegypti* infected with the bacteria to sterilize the mosquitoes. EPA should develop GE-specific regulations for evaluating GE insects under FIFRA; this should include requirements to demonstrate the environmental safety of the GE animals case by case and parallel case by case requirements for animal and human trials to demonstrate the efficacy of the kind of genetic engineering being used on human and animal health.

H. FDA Should Reinstate the Requirement for Public Hearings of Each New Kind of Genetically Engineered Animal.

The 2009 version of Guidance #187 was changed in June 2015 without any public comment to eliminate the public hearings. The original read:[16]

> The agency is interested in increasing the transparency of its deliberations and actions. At present, we intend to hold public advisory committee meetings prior to approving any GE animal. We may revisit that policy in the future as we gain more experience with reviews of GE animals.

GE animals are a controversial and novel use of biotechnology for which we do not have adequate risk assessment protocols. There are currently no GE animals in the food supply and only one that has been approved, and the legality of that approval is currently being reviewed by the courts. As such, the American public deserves to know if and when FDA is considering any GE animal approvals as soon as possible and as publicly as possible, with full transparency. The opaque nature of the GE animal review process underscores how ill-suited it is for the task. Public meetings should be mandated for any GE animals being considered, as early as possible.

Submitted by,

Center for Food Safety
International Center for Technology Assessment
Foundation Earth

---

[15] Columbia University Medical Center. "CRISPR gene editing can cause hundreds of unintended mutations." ScienceDaily. ScienceDaily, 29 May 2017, www.sciencedaily.com/releases/2017/05/170529111228.htm; Kellie A Schaefer, Wen-Hsuan Wu, Diana F Colgan, Stephen H Tsang, Alexander G Bassuk, Vinit B Mahajan. Unexpected mutations after CRISPR–Cas9 editing in vivo. Nature Methods, 2017; 14 (6): 547 DOI: 10.1038/nmeth.4293.
[16] FDA Guidance 187, 2009, p.11.