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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Submitted via http://www.regulations.gov

This letter provides comments to Docket No. FDA-2008-D-0394.

FDA Must Revise Current Regulatory Proposal for Gene-Edited Animals

On January 19, 2017, FDA published and invited comment on a document titled "Guidance for Industry, Regulation of Intentionally Altered Genomic DNA in Animals, Draft Guidance." FDA described it as "a revision of Guidance #187, 'Regulation of Genetically Engineered Animals,' … revised to update information concerning the products of different technologies used to produce such animals."[1] FDA states it "is intended to clarify our requirements and recommendations for producers and developers ('sponsors,' 'you') of animals with intentionally altered genomic DNA" and that it:

> "… addresses animals whose genomes 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 guidance applies to the intentionally altered genomic DNA in both the founder animal in which the initial alteration event occurred and the entire subsequent lineage of animals that contains the genomic alteration."[2]

[1] "Regulation of Intentionally Altered Genomic DNA in Animals Draft Guidance," (U.S. Food and Drug Administration, Guidance for Industry no. 187, January 15, 2009), http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm113903.pdf.
[2] Ibid.

This proposal is ill considered and counterproductive, and non-compliant with fundamental principles of U.S. regulation for biotechnology products laid down in 1986.[3]

FDA states clearly that this guidance is intended to cover the spectrum of so called "gene-editing" technologies that have exploded in recent years, specifically including CRISPR, but also noting that "other technologies intended to alter genomic DNA will arise over time" and would also be captured. FDA grounds their authority in the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321 et seq.) language concerning new animal drugs:

> "The term 'new animal drug' means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed, the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective…."

That broad definition makes it clear Congress intended to give FDA expansive authority, and with the established precedent of courts deferring to agencies in their construction of their authorities, it is likely that FDA's authority to advance this proposal would be upheld if challenged. It therefore appears that the FDA proposal is within its statutory authority. Whether or not it is wise, and whether or not it meets the criteria laid down by the White House Office of Science and Technology Policy (OSTP) in 2015, and is consistent with the 1986 Coordinated Framework, requires a closer look.

FDA does clarify that "in certain circumstances, based on the risk(s) they pose, we intend to exercise enforcement discretion with regard to … requirements for certain of these animals (that is, in specified circumstances, we do not intend to enforce the INAD and NADA requirements … " and require premarket approval. Exempted categories include non-food producing animals that are regulated by other agencies (like insects regulated by the Animal and Plant Health Inspection Service), animals used for research in contained facilities, as well as "other kinds or uses of animals based on our evaluation of risk factors." This seems reasonable. But FDA then lays out a process for review and approval of organisms whose genomes have been "intentionally altered" with newer breeding technologies (or, in fact, any means whatsoever). This is not so reasonable.

[3] Office of Science and Technology Policy (OSTP), "Update to the Coordinated Framework" (OSTP, 1992, 57 FR at 6753).

This proposal may be consistent with FDA's authorities, but to exercise this authority over a category that bears no demonstrable or meaningful relationship to hazard or risk is a fundamental departure from longstanding U.S. policy. In the absence of any finding of hazard and elevated risk associated with the regulated categories compared to others not captured, the imposition of far-reaching regulatory control measures, as the revised 187 guidance would impose, is not justified. To justify such a radical departure from fundamental principles, FDA would have to provide a persuasive case for the existence of hazards that would lead, if not regulated, to "unreasonable risks" to human or environmental health. This FDA has not shown.

A concrete example illuminates the problem.[4] Some cattle have horns, while others do not. Both traits are widely distributed among bovine lineages. Dairy cattle, selected for millennia to be optimal milk producers, generally have horns. This adds a counterproductive element of hazard to dairy operations, and so the practice of de-horning dairy cattle is widespread. The resulting reduction in risk to humans is significant, but the animal welfare costs are non-trivial, and many dairy farmers would love to find a better way to dispense with horns. Gene editing has provided a solution that is widely lauded as superior, humane, and urgently needed.[5] While the usual opponents of agricultural innovation remain hostile, there is little doubt it would be welcomed by dairy farmers.[6] University researchers, however, were dismayed at FDA's proposed rule, which creates unjustified impediments to such innovations despite the fact that all the DNA and proteins involved have been part of the human food chain since the dawn of civilization, and there is no plausible hypothesis of risk.[7] Widely reported as a "crackdown" on new animal breeding technologies, objections to this proposal have been immediate and widespread.[8] As animal biotechnology expert and U.C. Davis Professor Alison Van

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[4] Alison Van Eenennaam, "FDA Seeks Public Comments on Regulation of Genetically Altered Animals," *BioBeef Blog*, January 22, 2017, http://biobeef.faculty.ucdavis.edu/2017/01/22/fda-seeks-publiccomments-on-regulation-of-genetically-altered-animals.

[5] Daniel F. Carlson et al., "Production of Hornless Dairy Cattle from Genome-Edited Cell Lines," *Nature Biotechnology* 34 (May 6, 2016): 479–481, http:dx.doi.org/10.1038/nbt.3560.

[6] Kat McGowan, "This Scientist Might End Animal Cruelty—Unless GMO Hardliners Stop Him," Mother Jones, September/October, 2015, http://www.motherjones.com/environment/2015/07/fahrenkrug-genetic-modification-gmo-animals.

[7] Van Eenennaam, "FDA Seeks Public Comments on Regulation of Genetically Altered Animals."

[8] Kristen V. Brown, "The FDA's Newly Proposed GMO Rules Are Nonsense," *Gizmodo*, January 24, 2017, http://gizmodo.com/the-fdas-newly-proposed-gmo-rules-are-nonsense-1791519749; Ron Bailey, "Scientifically Absurd Proposed FDA Regulations on Genetically Improved Livestock Should Be Withdrawn Immediately," *Reason*, January 25, 2015, https://reason.com/blog/2017/01/25/scientificallyabsurb-proposed-fda-regul; Amy Maxmen, "Gene-Edited Animals Face US Regulatory Crackdown," *Nature News*, January 19, 2017, http://www.nature.com/news/gene-edited-animals-face-us-regulatorycrackdown-1.21331.

Eenennaam notes, FDA proposes to require that "each specific genomic alteration is considered to be a separate new animal drug subject to new animal drug approval requirements." What does this mean? She explains that:

> "[E]very [single nucleotide polymorphism] is potentially a new drug, if associated with an intended alteration…. To put this in perspective, in one recent analysis of whole-genome sequence data from 234 taurine cattle representing 3 breeds, >28 million variants were observed, comprising insertions, deletions and single nucleotide variants. A small fraction of these mutations have been selected owing to their beneficial effects on phenotypes of agronomic importance. None of them is known to produce ill effects on the consumers of milk and beef products, and few impact the well-being of the animals themselves."

By contrast to FDA's proposal, guidance that would be consistent with three decades of U.S. policy and the 2015 OSTP mandate to review and update, FDA could have asserted its jurisdiction as they have done, but announced that, in keeping with longstanding policy, they would exercise discretion and not routinely recommend (much less require) consultation from developers. They would have had then a strong basis to invite public comment to help in defining categories of intentional genomic alterations of potential concern that could present unreasonable risks sufficient to justify consultation, and even possibly further regulatory action. This would have been reasonable, consistent with millennia of experience as well as our most up-to-date understanding of modern molecular biology, and defensible as policy.[9] It is not too late to get it right.

By contrast, in the matter of gene-edited mosquitoes intended to address diseases such as Zika, Dengue, Chikungunya, and others carried by their primary insect vector, *Aedes aegypti,* FDA has prudently stepped back from regulating and deferred to the Environmental Protection Agency (EPA).[10] This mosquito species appears to play an essential role in no ecosystem on earth, and in the Americas it is an invasive, colonizing species.[11] Its role as a vector of numerous human diseases and apparent lack of any signal virtues has led to

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[9] Werner Arber, "Genetic Engineering Compared to Natural Genetic Variations," *New Biotechnology* 27, no. 5 (2010): 517–521, http:dx.doi.org/10.1016/j.nbt.2010.05.007.

[10] "Mosquito Borne Disease," Oxitec, Ltd., accessed March 14, 2017, http://www.oxitec.com/mosquitoborne-disease.

[11] Sir S. Rickard Christophers, "Aedes Aegypti (L.)," in *The Yellow Fever Mosquito: Its Life History, Bionomics, and Structure* (NY: Cambridge University Press, 1960), pp. xii, 739.

calls for its complete extirpation as the deadliest animal on the planet.[12] This is the animal for which the term "pestilential" was coined.

As FDA made clear in its 187 Guidance document, gene-edited versions of this mosquito meet the legal definition of an "animal drug." But in declining to regulate the gene-edited variety developed to suppress human disease transmission, FDA has merely deferred to congressional intent, which defines it as a pesticide when "the product is intended to reduce the population of mosquitoes and does not make a disease prevention claim." So the real credit for this must be chalked up to Congress. It will be important to track this closely to make sure that EPA does not stifle this innovation.

FDA should dramatically revise the present proposal, and develop a new proposal laying out their authority to regulate, and invite comment on their intention to exercise discretion for the products of modern genome modification techniques; FDA should invite comments to help define phenotypic categories of intentionally modified animals that represent potentially elevated hazard to human health or animal, welfare which may be appropriate subject of regulatory oversight, based on data and experience.

Sincerely,

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[12] Bill Gates, "The Deadliest Animal in the World," *GatesNotes*, April 25, 2014, https://www.gatesnotes.com/Health/Most-Lethal-Animal-Mosquito-Week; Daniel Engber, "Let's Kill All the Mosquitoes," *Slate*, January 29, 2016, http://www.slate.com/articles/health_and_science/science/2016/01/zika_carrying_mosquitoes_are_a_global_scourge_and_must_be_stopped.html.