A Greener World-American Anti-Vivisection Society-Animal Legal Defense Fund
Animal Welfare Institute-Center for Food Safety-Food and Water Watch
Food Animal Concerns Trust-Friends of the Earth-Institute for Agriculture and Trade Policy
International Center for Technology Assessment-National Family Farm Coalition
Northwest Atlantic Marine Alliance-World Animal Protection

Secretary Tom Vilsack
U.S. Department of Agriculture
1400 Independence Ave., SW
Washington, DC 20250

April 5, 2021

Dear Secretary Vilsack:

Sent by mail and by email

RE: Movement of Regulation of Animals Modified or Developed by Genetic Engineering to USDA

Congratulations on your confirmation as Secretary of Agriculture by the Senate.

We are consumer, animal welfare, food safety, agriculture trade policy, and environmental groups concerned about the food safety, environmental, and animal welfare effects of genetically engineered food animals.

We wish to bring to your attention an administrative action by outgoing Secretary of Agriculture Sonny Perdue to withdraw most of FDA's regulatory authority over genetically engineered animals and fish and transfer that authority to the Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). The administrative action takes the form of a Memorandum of Understanding (MOU) signed on January 13, 2021 by Secretary Perdue and Dr. Brett Giroir, HHS Assistant Secretary for Health, and posted on the APHIS website. [1]

On January 11, FDA Commissioner Hahn told HHS that he refused to sign the MOU, according to *Politico*, "amid concerns about its legality and the potential health repercussions of relaxing oversight of certain genetically altered products. . . . One senior administration official told POLITICO that the White House was behind the sudden push for approval." Career FDA lawyers opposed the MOU, but they were overruled by HHS political appointees. [2] The MOU is part and

[1] Memorandum of Understanding Between the United States Department of Agriculture and the Food and Drug Administration, Department of Health and January 13, 2021 available at: https://www.aphis.usda.gov/biotechnology/downloads/mou-usda-fda.pdf

[2] Sara Owermohl and Adam Cancryn, "FDA fights for independence in Trump administration's final days," *Politico*, January 13, 2021. https://www.politico.com/news/2021/01/12/fda-independence-hhs-458515

USDA responses to this letter can be sent to jhanson@centerforfoodsafety.org 703-231-5956

parcel of other Trump administrative initiatives to weaken FDA's authority to protect public health.

We share Commissioner Hahn's concerns and urge you to instruct USDA officials to remove the MOU from the APHIS website as the MOU is invalid.

Secretary Perdue, in announcing the MOU, repeated animal and meat industry arguments that FDA's safety-oriented regulatory approach impedes rapid commercialization of GE animals. The industry demands, in the words of the National Pork Producers Council, "regulatory certainty" to expedite investment in and commercialization of GE animals, especially swine. [3] However, reassigning regulatory authority to an agency avid to market GE animal products world-wide represents a conflict of interest and very likely could compromise the scientific integrity of the risk assessment of novel GE animals.

FDA found compelling grounds for stringent oversight of newer GE techniques. For example, in the case of the GE "hornless" dairy cow developed by the Minnesota firm Recombinetics. The USDA had been touting the gene editing used to produce the "hornless" (polled) cow as being just like conventional breeding, only faster. The company insisted that it had examined the genomic sequence of the animal and found no unintended effects. Fortunately, FDA scientists examined the sequence of the animal and found that the engineering had left a full copy of a plasmid and a second copy of the repair template sequence in the genome, making this a transgenic animal. [4] The plasmid, which contained genes for resistance to the antibiotics ampicillin, neomycin and kanamycin, was used to edit the DNA but should not have been left behind in the genome of the animal. Why hadn't Recombinetics found this inserted genetic material which FDA scientists found? Because, according to the CEO of the Recombinetics subsidiary that engineered the GE hornless cattle, the company had never bothered to look for the genetic sequence of the plasmid since they did not think that it would be integrated into the genome of the cow. [5]

USDA and Recombinetics both should have known that gene editing techniques, such as use of engineered nucleases, are known to cause off-target mutations and can cause even on target problems. Studies with mouse cells have shown that CRISPR-Cas9 not only causes off-target mutations, [6] it also can lead to on-target mutations that can lead to large deletions and complex

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[3] Dan Flynn, "Perdue exits the building after getting USDA jurisdiction over gene-edited livestock," *Food Safety News*, January 22, 2021. https://www.foodsafetynews.com/2021/01/perdue-exits-the-building-after-getting-usda-jurisdiction-over-gene-edited-livestock/

[4] Norris AL, Lee SS, Greenlees KJ, Tadesse DA, Miller MF and H Lombardi. 2020. Template plasmid integration in germline genome-edited cattle. *Nature Biotechnology*, 38: 163-164.

[5] "It was not something expected, and we didn't look for it" says Tad Sontesgard, CEO of Acceligen, a subsidiary of Recombinetics that owns the animals.
Regaldo, A. 2019. Gene-edited cattle have a major screwup in their DNA. MIT Technology Review. At: https://www.technologyreview.com/2019/08/29/65364/recombinetics-gene-edited-hornless-cattle-major-dna-screwup

[6] Yee J-K. 2016. Off-target effects of engineered nucleases. *The FEBS Journal* 283:3239-3248. At: https://febs.onlinelibrary.wiley.com/doi/pdf/10.1111/febs.13760

chromosomal rearrangements. [7] Another mouse study using CRISPR-Cas9 found large on-target mutations that resulted in immune dysregulation. [8] In June 2020, *Nature* published a story on three studies involving human embryos that all found large unwanted on-target mutations involving large deletions and chromosomal rearrangements, and even referred to these effects in the headline as "chromosomal mayhem." [9] Clearly, gene editing techniques can cause both on-target and off-target effects, with potentially adverse consequences. Fortunately, FDA's draft guidance on new kinds of genetic engineering would at least have the producer of a new animal demonstrate that there are no "off target" effects. [10]

These unsettling and unanticipated safety issues underscore both how much there is yet to learn about manipulating the genomes of animals, as well as the need for "safety first" regulation. Undoubtedly, FDA, the nation's food and drug safety authority, is better equipped to fulfill this role than USDA.

USDA's track record in this arena also speaks against investing it with regulatory authority over GE animals and fish. First, the Department's Animal and Plant Health Inspection Service (APHIS) declined to develop extensive regulations to oversee genetically engineered animals and developed only limited protocols to govern scientists' research on GE animals and insects, despite explicit recommendations from the USDA Inspector General to develop regulations. Moreover, in its response to the Inspector General, the USDA staff said that the FDA review of GE animals was scientifically robust, *"We wish to emphasize that the Food and Drug Administration (FDA) now has a rigorous mandatory approval process for GE animals that examines, among other things, the health of the animal. As described in the OIG report, FDA published Guidance to the Industry which describes how FDA's New Animal Drug Authority will be used to evaluate the safety of GE animals."* [11]

FDA scientists have demonstrated that they intend to take a fulsome approach to reviewing GE animals. FDA has adopted a scientifically sound definition of genetic engineering that includes newer gene-editing techniques – bucking the pressure from industry players to have gene-editing declared exempt from GE regulation. This definition is also in line with that of many other nations, including those of the European Union, [12] promoting harmonization with key trade partners.

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[7] Kosicki M, Tomberg K and A Bradley. 2018. Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology*. Doi:10.1038/nbt.4192. At: https://www.researchgate.net/publication/326429946_Repair_of_double-strand_breaks_induced_by_CRISPR-Cas9_leads_to_large_deletions_and_complex_rearrangements

[8] Simeonov DR, Brandt AJ, Chan AY, Cortez JT et al. 2019. A large CRISPR-induced bystander mutation causes immune dysregulation. *Communications Biology* 2:70. At: https://www.nature.com/articles/s42003-019-0321-x.pdf

[9] Ledford, H. 2020. CRISPR gene editing in human embryos wreaks chromosomal mayhem. Nature 583: 17-18. At: https://www.nature.com/articles/d41586-020-01906-4

[10] FDA. 2017. Draft Guidance for Industry #187 Regulation of Intentionally Altered Genomic DNA of Animals. At: https://www.fda.gov/media/74614/download

[11] https://www.aphis.usda.gov/biotechnology/downloads/audits/USDA_OIG_50601-16-Te.pdf

[12] Center for Food Safety, Comments on USDA's regulatory changes, August 6, 2019. https://www.centerforfoodsafety.org/files/part-340-comments--center-for-food-safety--2019-08-06_34160.pdf.

In brief, we believe it is clear that FDA has far more of the expertise and "safety first" perspective needed to regulate novel GE animals. Stringent regulation is required not only to ensure safety, but also to avoid blowback from the "rush-to-market, consequences be damned" mentality of some biotechnology enthusiasts. That said, FDA needs to shore up its regulatory regime. Guidance documents for GE animal regulation should be recast as formal regulations capable of addressing, with appropriate monitoring and enforcement procedures, the food safety and the environmental safety challenges posed by these new kinds of genetically engineered organisms.

With such improvements, FDA is the clear choice for regulating GE animals. **We request that you withdraw from the APHIS website the Memorandum of Understanding that would transfer GE animal review to the USDA. We also request a meeting with APHIS biotechnology staff to discuss this memorandum and their biotechnology review of other GE organisms, including insects.**

Sincerely,

Jaydee Hanson, Policy Director, Center for Food Safety jhanson@centerforfoodsafety.org

On behalf of:

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Animal Legal Defense Fund
Animal Welfare Institute
Center for Food Safety
Food and Water Watch
Food Animal Concerns Trust (FACT)
Friends of the Earth
Institute for Agriculture and Trade Policy
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