June 19, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2008-D-0394: Regulation of Intentionally Altered Genomic DNA in Animals; Draft Guidance for Industry; Notice of Availability

To Whom It May Concern:

The North American Meat Institute (NAMI or the Meat Institute) submits these comments about the above-referenced draft guidance on altering genomic DNA (gene editing), issued by the Food and Drug Administration (FDA or the agency). Formed from the merger of the American Meat Institute and North American Meat Association, the Meat Institute has a rich, century-long history and provides essential member services including legislative, regulatory, scientific, international, and public affairs representation for the meat and poultry packing and processing industries. Together, NAMI members produce the vast majority of U.S. beef, pork, lamb, and poultry products in the United States.

The agency must understand the implications of regulating gene-edited animals as animal drugs before this guidance is implemented.

FDA should carefully consider the implications of regulating gene editing technology as a drug subject to the recommendations proposed in Draft Guidance for Industry #187. Gene editing technology has significant potential to positively affect food animal health, welfare, and productivity. Under the proposed regulations, all living, breathing animals with even a single base pair deletion or edit due to this technology *and* all their offspring would be considered animal drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act).

The FD&C Act defines drugs as: "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." [1] Under this definition, every new gene edit would be a new animal drug and therefore would have to go through the New Animal Drug Application (NADA) process. The term "articles," however, is not defined by FDA, and could be limitless in its application to specific changes to the structure or function of the body of man or animals. Indeed, if the term "articles" is extended to applying surgical procedures or selective breeding techniques, potentially all changes made, artificially or naturally, to man or animals could be an "article" and subject to the recommendations proposed in this guidance document, making regulation of any "drug" impossible.

Changes to structure and function food animals occur naturally as phenotypic expressions of gene mutations, and can improve animal health, animal welfare, food safety, and even public health. A number of the alterations proposed for use by gene editing are modeled after naturally-occurring genetic mutations.[2,3] If the changes introduced by alterations can be caused by natural mutations, it will be impossible to determine which animals contain the naturally-occurring mutation versus those with the mutation produced by altering the genome. And while many changes introduced via gene editing can be introduced through the natural breeding of animals, costs would be much higher, and the outcomes may require years or decades to come to fruition, which is why this technology is so valuable to the food animal industries.

Applying gene editing technologies to animals used for the production of biopharmaceuticals or medical devices may fall under the draft guidance of this document or others listed. However, the regulations in this guidance would also extend to the application of gene editing to food animals strictly for disease and pest mitigation, improvement of animal welfare, or production purposes. Such an application may not be appropriate, especially in large animal populations.

---

[1] Section 201(g) of the Food, Drug, and Cosmetic Act gives the definition of a drug as: "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."

[2] Van Breedam W, Delputte P, Van Gorp H, et al. 2010. Porcine reproductive and respiratory syndrome virus entry into the porcine macrophage. *J Gen Virol* 91: 1659-1667.

[3] Carlson DF, Lancto CA, Zang B, et al. 2016. Production of hornless dairy cattle from genome-edited cell lines. *Nature Biotech* 34: 479-481.

Regulating gene-edited animals as animal drugs can harm the food animal industries.

Regulating gene editing technology as presented in the draft guidance will likely create several potential barriers to live animal production, domestic and international trade, and overall consumer acceptance of products from animals under this regulatory umbrella. The burden of record-keeping, reporting, monitoring, and enforcement the agency would experience must also be considered.

In the draft guidance, the agency states animals with intentionally altered genomes are subject to the premarket approval requirements of animal drugs, including the NADA requirements.[4] A New Animal Drug Application can be expensive, and in the case of application to live animal production, likely time-consuming and labor-intensive. The delay in use caused by the application process may delay many positive outcomes gene editing can bring to the animal health population, including disease prevention and treatment strategies.

Applying these recommendations to both founder animals and the entire later lineage of animals containing the genomic alteration will also be time-consuming and labor-intensive, if not more burdensome, than the application process. For example, the guidance provides proper labeling, including animal care and safety information, must accompany *all* animals throughout *all* stages of their lifecycles.[5] This requirement creates the potential for millions of drug labels accompanying millions of animals through different production phases, including transport, all over the country, and leads to questions on further follow-up. The term "lifecycle" is not defined in the current or revised guidance, nor in any current regulation, therefore it is unclear whether the drug label must follow an animal through processing to consumer products. Although common sense suggests such labeling stop at the point the animal is deceased, clarification is needed to determine how products from gene-edited animals will be labeled before and after harvest for food production.

The guidance provides no information on applying other regulations in the Act, such as addressing residues that cannot be cleared because they are a part of the animal's genome.[6] FDA also monitors and encourages reporting of adverse events in relation to administration of animal drugs.[7] What is FDA's definition of an adverse event in such animals? And does the agency intend to monitor every adverse event in

---

[4] FDA Draft Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals, p. 8.
[5] *Id.* p. 16
[6] 21 CFR 514.1 (a)(7)
[7] U.S. Food and Drug Administration website: https://www.fda.gov/animalveterinary/safetyhealth/reportaproblem/ucm055305.htm. Accessed June 6, 2017.

every founder animal and its offspring (potentially millions of animals) that could be due to an altered genome, even if the event is not related to the edited portion of the genome?

Treating these animals as drugs also will likely have a negative impact on domestic and international trade. The movement of live animals across U.S. borders might be deemed importation or exportation of animal drugs, and may be regulated in an entirely different way compared to current live animal import or export. Such an application would create overwhelming trade barriers for importers and exporters of live animals. The acceptance of animals and animal products from gene-edited animals, especially if products are also considered animal drugs, could be low to non-existent in importing countries, especially those that impose a zero-tolerance standard for many animal drugs used in the U.S. Even domestically, labeling animals as drugs could negatively affect consumer acceptance of animal products from those animals, besides any other potential labeling requirements regarding the animal's status as gene-edited.

The agency's proposed recommendations are inconsistent with other global regulatory trends regarding this technology.[8] For example, while the European Union has yet to decide how it will regulate gene-edited plants, Sweden and Finland remain in favor of non-regulation until the final decision on a common form of regulation is made.[9] Canada regulates its genetically-engineered crops on the basis of their attributes rather than the process used to generate them.[10] If these countries extend such regulation to the use of gene-editing in animals, the regulations proposed by the FDA to gene-edited animals in the U.S. could hinder our country's ability to keep up with global trends in technology and trade.

Finally, the time, labor, and monetary resources needed to accommodate the additional monitoring, reporting, and enforcement of the recommended practices will be an enormous burden to the agency, and may not be available without placing further economic burden on the food production industries. The draft guidance fits the Office of Budget and Management's definition of a "Significant Guidance Document," which states

> "…for purposes of Executive Order 13771, a significant guidance document is a *guidance document* disseminated to regulated entities or the general public that may *be reasonably anticipated* to lead to an annual effect on the economy of $100 million or more or *adversely affect in a material way the economy, a*

[8] Foreign Agricultural Services, personal communication
[9] *Nature* 542, 392 (23 February 2017). doi: 10.1038/542392a.
[10] *Nature* 546, 327-328 (15 June 2017). doi: 10.1038/546327b.

sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local or tribal government communities…"[11]

The agency should consider the possibility that the economic burden placed on the food animal, genetics, and pharmaceutical industries by the proposed regulations would be enough to support repealing the guidance.

* * * * *

The Meat Institute urges FDA to consider all options as it develops guidance on gene editing, especially its use in the food animal production industries. This technology is too valuable to ignore the potential implications of these recommendations on live animal production, domestic and international trade, and economic burden on the industries.

I would be happy to discuss these comments, the Meat Institute's position regarding the Draft Guidance, or questions you have.

Respectfully submitted,

Tiffany Lee, DVM
Director
Regulatory and Scientific Affairs

cc:

Barry Carpenter
Mark Dopp
Bill Westman
Janet Riley
Norm Robertson
Susan Backus
KatieRose McCullough, PhD
Eric Mittenthal

[11] Memorandum for Regulatory Policy Officers at Executive Departments and Agencies and Managing and Executive Directors of Certain Agencies and Commissions. Guidance Implementing Executive Order 13771, Titled "Reducing Regulation and Controlling Regulatory Costs. Issued April 5, 2017. https://www.whitehouse.gov/the-press-office/2017/04/05/memorandum-implementing-executive-order-13771-titled-reducing-regulation. Accessed June 7, 2017 (emphasis added).