National Milk Producers Federation

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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Re: FDA-2008-D-0394: Regulation of Intentionally Altered Genomic DNA in Animals; Draft Guidance for Industry; Notice of Availability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 National Milk Producers Federation (**NMPF**) is pleased to submit the following comments to the Food and Drug Administration (**FDA**) on the January 19, 2017 draft revisions to FDA Guidance for Industry #187 *Regulation of Intentionally Altered Genomic DNA in Animals (***GFI #187**). The National Milk Producers Federation, established in 1916 and based in Arlington, VA, develops and carries out policies that advance the well-being of dairy producers and the cooperatives they own. The members of NMPF's cooperatives produce the majority of the U.S. milk supply, making NMPF the voice of dairy producers on Capitol Hill and with government agencies like USDA. NMPF provides a forum through which dairy farmers and their cooperatives formulate policy on national issues that affect milk production and marketing.

U.S. dairy farmers see unique potential in gene editing to address animal health issues, as well as assisting the industry in making continuous improvement in areas such as animal welfare, responsible antibiotic use, and sustainability. An appropriate and practicable regulatory environment is necessary to ensure that this potential can be realized. Therefore, NMPF requests FDA to reconsider the proposed regulatory framework for gene editing as it relates to food animals.

FDA should look to the 2017 National Academies of Sciences, Engineering and Medicine report *Preparing for the Future Products of Biotechnology* (**NAS Report**)[1] for direction on revising GFI #187. NMPF requests that FDA acknowledge that not all gene editing applications to animals require approval as new animal drugs under the Food, Drug and Cosmetic Act (**FD&C Act**). Such an interpretation of the **FD&C Act** —especially as applied to many potential uses of gene editing techniques in livestock— mischaracterizes resultant edited genomes as an "***article***", creating potentially insurmountable practical barriers to enforcement by FDA and utilization by industry. This is not in keeping with federal policy and precedence—and indeed global regulatory

[1] National Academies of Sciences, Engineering, and Medicine. 2017. Preparing for Future Products of Biotechnology. Washington, DC: The National Academies Press. doi:https://doi.org/10.17226/24605.

trends—concerning the use of biotechnology in agriculture. Furthermore, it does so without any appreciable benefit to animal or public health. NMPF recognizes that FDA has an interest under the FD&C Act in the application of gene editing techniques to animals intended to produce biopharmaceuticals or medical devices, and that FDA's current proposal may be appropriate to this specific application.

The NAS Report offers a clear and elegant pathway, consistent with the *Coordinated Framework for the Regulation of Biotechnology* (**Coordinated Framework**)[2], that FDA can utilize to determine what, if any, approval under the FD&C Act is required for gene edited animals not intended to produce biopharmaceuticals or medical devices. This regulatory approach would utilize the NAS Report's elegant classification system of new biotechnology products as "familiar and noncomplex", "unfamiliar or complex", and "unfamiliar and complex". Rather than requiring a new animal drug application for each gene edit to animals, NMPF proposes that FDA institute a notification process whereby the developers of gene edited animals inform FDA of the technical nature of the genetic edit (quantitative and qualitative descriptors of factors such as the source, size, and method of the edit) so that FDA can expeditiously and predictably categorize and take appropriate action as follows:

- **Familiar and Noncomplex: The nature of the gene edit is such that it either corresponds to a genotype found in the subject or a sexually compatible species, could reasonably occur in the subject species through mutagenesis, or is a deletion of any size**. Animals produced through gene editing techniques that meet these criteria should not be subject to regulation under the FD&C Act. The inserted or deleted genetic sequences, or the resultant genome, cannot be defended as an "article" under the FD&C Act. Animals derived from gene edits that fall into this category would have a genome indistinguishable from non-genome edited animals that share the relevant genotype through inheritance or mutagenesis. Therefore, they and products they produce pose no novel risks. The consideration of their genome as a new animal drug—in perpetuity under the GFI #187—cannot be defended on scientific, practical, or public health grounds. FDA should inform the developer in writing that the resultant animals will not be regulated under the FD&C Act, and that any products produced by these animals will not be subject to any additional scrutiny under the FD&C Act than they would be accorded if from non-gene edited animals.

- **Unfamiliar or Complex: The inserted genetic material is limited to one or a few genes that are not reasonably likely to occur in the subject species, or consists of multiple and interacting familiar genes.** Animals produced through

[2] https://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf

gene editing techniques that meet these criteria should be subject to a test to determine the appropriateness of regulation under the FD&C Act. FDA should develop a modified approval process whereby the novelty of the edit can be assessed against previous applications and the safety of the edit can be demonstrated as appropriate. The "article" under the FD&C Act in this circumstance should be limited solely to the genetic information inserted into the animals subject to the gene editing technique—the genetic inheritance of their offspring and further descendants should not be considered an "article" under the FD&C Act, and they or their products should not be subject to any special consideration or labelling under such.

- **Unfamiliar and Complex: The inserted genetic material is not reasonably likely to occur in the subject species and consists of multiple interacting genes.** Animals produced through gene editing techniques that meet these criteria may be the proper subject of regulation under the FD&C Act under a framework similar to that proposed in GFI #187. However, FDA should develop a clear pathway by which after a defined number of generations—a number reasonable to demonstrate safety and efficacy—their descendants not produced through gene editing techniques cease to have their genomes considered an article of interest under the FD&C Act, or their products subject to any additional scrutiny or labelling under such.

NMPF believes that this approach is defensible under the Coordinated Framework, and is legally and scientifically defensible. It relies on the best and most current guidance available to FDA as found in the NAS Report. The regulatory pathway proposed by FDA in GFI #187—though it may be appropriate to some animals produced through gene editing techniques—cannot be legitimately applied to all circumstances. NMPF offers the following additional information in support of this position:

- **The genotype resulting from gene edits determined to be "familiar and noncomplex" could legitimately and reasonably be achieved through current animal breeding techniques.**

Gene editing offers the animal agriculture community incredible promise to rapidly disseminate desirable characteristics through animal populations. Gene edits that are familiar and complex either mimic genetic sequences known to exist in the species of interest, or that are very reasonably likely to exist or to develop through mutagenesis with or without selection pressure. These genes could be propagated without gene editing techniques—though at a much slower rate and not in isolation thereby compromising years of selective breeding—throughout the species.

Given the known nature of this genetic material—or in the case of a deletion the high predictability of the result—there is no new or novel element being introduced into the genetic library of the subject species. There is therefore no new or novel risk or threat to animal health, human health and food safety, or the environment. The use of gene editing in this context should not be viewed in a regulatory capacity as any different from those already in use developed over millennia of domestication. Any special scrutiny or labelling would be without scientific or legal merit.

- **Any DNA sequence that is deleted from, or that is naturally found or is reasonably likely to be found in a species' natural genome, does not meet the statutory definition of a "drug" as defined in section 201(g) of FD&C Act.**

GFI #187 cites its authority to section 201(g) of the Federal Food, Drug and Cosmetic Act (FD&C Act). Section 201(g) defines 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." FDA GFI #187qualifies its authority on the basis that "altered genomic DNA in an animal is a drug within in the meaning of section 201(g) of the FD&C Act because such altered DNA is an article intended to affect the structure or function of the body of the animal, and, in some cases, intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in the animal." However, FDA's logic fails when applied to situations where gene-editing techniques are utilized to delete DNA and when DNA that would naturally be found, or is reasonably likely to be found in the species genome is inserted.

The FD&C Act's definition for "drug" is inherently premised on the idea that an "article" is foreign and distinct from the recipient and therefore is a necessary addition to induce a change to the structure or function of man or animal. When gene editing techniques are utilized to delete DNA, there is no distinctive article, as defined in GFI #187, added to cause the resulting change to the structure or function of the animal.

Further, altered genomic DNA that could naturally be found, or that is reasonably likely to be found, in the natural genome of the species is not a foreign or distinct article. This logic is harmonious with the commonly used definition of "article,"[3] which is defined as: "a thing or person of a distinctive kind or class,"[4] and the commonly used definition of "thing" is: "a separate and distinct individual quality, fact, idea or usually."[5]

[3] The FD&C Act does not define "article[s]." *See* 21 U.S.C. § 321.
[4] Merriam-Webster Dictionary, https://www.merriam-webster.com/dictionary/article (last visited June 19, 2017).
[5] Merriam-Webster Dictionary, https://www.merriam-webster.com/dictionary/thing (last visited June 19, 2017).

When gene editing is used to delete DNA and when gene editing is used to insert DNA that is naturally found, or is reasonably likely to be found in the species genome, there is no foreign or distinct article; consequently, there is no "drug" as defined in the FD&C Act.

- **There are real and significant barriers to FDA's proposed regulatory pathway that would consider a genome that had been subject to gene editing an animal drug in perpetuity. More simply put, we do not feel that FDA has properly explored or defended the concept of living, breathing "animal drugs" requiring its unending oversight.**

An animal's genome is a fundamental and indivisible component of its existence. Therefore, the consideration of any genome with an inherited legacy of gene editing as an animal drug means the animal is an animal drug; this is acknowledged by FDA in GFI #187.

The gene edits that we propose classifying as familiar and noncomplex have the potential to solve significant animal health, animal welfare, food safety and public health, sustainability, and other challenges. These challenges could be met through current animal breeding techniques, though at a much higher cost. This potential could lead to widespread adoption of gene editing in animal breeding. The result would be millions—or in the case of honey bees billions—of new "animal drugs" moving in commerce in the U.S. alone.

The ramifications of this are many and severe, and that is why in our counterproposal we recommend that FDA not use or at a minimum confine this designation to one or at most several generations. NMPF would like to highlight several ramifications as demonstrative of the non-viability of this position:

First, drug residues—how does FDA intend to apply existing regulations under the FD&C Act in this context? The paradox is that FDA will in fact have created a residue that cannot be cleared; yet if FDA exempts gene edited genetic material from consideration as a residue or considers it a residue of no risk it undermines the defensibility of its determination that it is an animal drug.

Second, adverse event reporting—how does FDA intend to monitor adverse events? How can any event—be it a phenotypic change, response to a disease challenge, or indeed any behavior not considered normal—be conclusively deemed the result of the application of gene editing techniques (which may be many generations removed) or indeed be considered not a potential consequence under the current adverse event

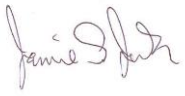
reporting parameters? Can FDA accommodate such an increase in reporting? Again, an exemption from this requirement challenges the underlying premise.

Third, and most crucially—has FDA considered the potential ramifications to both domestic and international trade in animals and animal products? There are hundreds of thousands of animals that move across the U.S. border every year. Will these now be considered imports or exports of animal drugs? What conditions will importers have to satisfy as to the regulatory oversight of the country of origin, and what trade barriers will U.S. exporters face, either in response or by existing regulation in the destination country not intended but still applicable to this scenario. And that is just live animals—the unnecessary threat that this approach aims at the multi-billion-dollar animal product trade is untenable.

NMPF strongly believes that it is indefensible for FDA to propose that all animals resulting from gene editing techniques be considered animal drugs in perpetuity through a guidance document. Should FDA remain committed to this approach—and it is our strong hope that it will not—a decision of this magnitude must be subject to rulemaking under the Administrative Process Act and FDA must undertake the required risk analysis and economic impact study with due diligence.

Thank you for your attention to our comments. Gene editing offers our and allied industries promising opportunities for continuous improvement in animal health, animal welfare, sustainability, and public health. We appreciate the newness of this technology, and that GFI #187 was a starting point for a discussion about regulation of this technology and not the final and absolute position of FDA. NMPF looks forward to working with FDA to develop a framework that will be defensible and workable. If you have any questions or require additional information, please contact me at 703-243-6111 or at jjonker@nmpf.org.

Sincerely,



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