April 25, 2017

FDA's Draft Guidance #187: Regulation of Intentionally Altered Genomic DNA in Animals

Summary Report

On January 19, 2017, the Food and Drug Administration (FDA) published in the *Federal Register* a notice of availability of a new draft guidance for industry (GFI) #187, entitled "Regulation of Intentionally Altered Genomic DNA in Animals," which revises GFI #187 entitled "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs." The revisions clarify FDA's requirements and recommendations for producers and developers of genetically engineered animals and their products.

The revised GFI expands the scope of the previous guidance to include animals intentionally altered through genome editing techniques. The revised GFI applies to "those animals whose genomes have been intentionally altered using modern molecular techniques."[1]

An example of these "modern molecular techniques" is the use of gene editing to help protect pigs from porcine reproductive and respiratory syndrome (PRRS) virus. Recent research explores the use of specific enzymes to break DNA at targeted locations in the genome and cause either deletions or insertions of other DNA, if provided.[2] These technologies introduce alterations at specific sites in the genome, rather than the more random changes that may come with recombinant DNA technology.

An effective approach to gene editing in pigs is the CRISPER/Cas9 system, which can alter the DNA that codes for the receptor CD 163.[3] Some have suggested

[1] Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals, Draft Guidance. Section I. Introduction and Background.
[2] Whitworth KM, Lee K, Benne JA, et al. 2014. Use of the CRISPR/Cas9 system to produce genetically engineered pigs from in vitro-derived oocytes and embryos. *Biol Repro*. 91(3): 1-13.
[3] Whitworth KM, Rowland RR, Ewen CL, et al. 2016. Correspondence to the Editor: Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus. *Nature*. 34(1): 20-22.

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that CD 163 is a receptor for entry of PRRS into macrophage cells, where they replicate and cause clinical disease.[4]

Gene editing was used in the research setting to mutate the CD 163 receptor and therefore block the entry of PRRS virus into cells of otherwise genetically normal pigs. The offspring of these gene-edited pigs also contain the mutation. Gene-edited offspring inoculated with the PRRS virus showed no viral replication or clinical signs of the disease, while inoculation of non-genetically-edited (wild-type) pigs resulted in virus replication and clinical signs of the syndrome.[5]

Although this technology is still in infant stages and additional research is warranted, it holds promise for successful disease intervention. Because the technology would be used in disease prevention practices, the altered genomic DNA in such animals meets the definition of a drug in section 201(g) of the Food, Drug, and Cosmetic Act.[6] Therefore, FDA considers each genomic alteration ("edit") as a separate new animal drug subject to new animal drug approval requirements, including application for approval of the new animal drug. In addition, if such animals are eventually intended for the food supply, an Investigational Food Use Authorization must be requested, and the Food Safety and Inspection Service (FSIS) must be informed of FDA's authorization of such use.[7]

The revised GFI also states "Where the labeling for an animal whose genome has been intentionally altered contains animal care or safety information (*e.g.*, husbandry or containment), we recommend that the labeling accompany the animal throughout all stages of its lifecycle."[8] The term "lifecycle" is not defined in the current or revised GFI, therefore it is unclear whether such labeling would follow an animal through processing to consumer products. Although common sense suggests the labeling stop at the point the animal is deceased, clarification is needed to determine how products from gene-edited animals will be labeled, and FDA's request for comments does not mention further labeling of pork products. Recommendations on labeling requirements may come from FSIS after more research is conducted.

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[4] 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.
[5] See Footnote 2: Whitworth, Rowland, Ewen et al.
[6] 21 U.S. Code § 321 Section 201 (g)(1)(B): The term "drug" means articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.
[7] Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals, Draft Guidance. Section III. C. Investigational Food Use Alterations.
[8] *Id.* Section IV. B. 3. Labeling.

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For now, FDA seeks the public's input on how to refer to gene-edited animals. In the past, FDA used the term "genetically engineered" to refer to animals containing changes via the rDNA technology. However, for the revised guidance, the phrase "animals whose genomes have been altered intentionally" is used. FDA encourages the public to suggest other phrases that are accurate and inclusive.

FDA also posed a set of questions and encourages public input. The questions focus on risks gene-edited animals may pose, the durability of the genomic changes, and degrees of the introduced changes. The questions are provided below.

1. Are there categories of animals whose genomes have been intentionally altered for which specific empirical evidence indicates there are no significant target animal, user safety, food safety, or environmental risks? If so, what is the evidence?
2. Are there categories of animals whose genomes have been intentionally altered for which empirical evidence exists to demonstrate that genome editing is durable on a genotypic and phenotypic level and would continue to be durable over the lifetime of a particular product? If so, what evidence?
3. Is there empirical evidence to demonstrate there are degrees of introduced changes (e.g., insertions or deletions of any size or single nucleotide substitutions) that are likely to pose less risk than other changes? If so, what evidence?
4. Is there empirical evidence that indicates that the degree of taxonomic relationship between the introduced gene and the recipient animal influences the health of that recipient animal or the extent to which the trait is expressed? If so, what is that evidence?

The original comment period was 90 days after publication in the *Federal Register*, or April 19, 2017. On April 12, 2017, the comment period was extended another 60 days to June 19, 2017. If you would like to provide input, please provide your information to the Meat Institute no later than May 26, 2017. If you have questions about the notice, this report, or anything else regarding this matter, please contact me at tlee@meatinstitute.org.

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