



# Animal Welfare Institute

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July 30, 2024

Docket No. FDA-2019-D-2648  
Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

*Submitted via Regulations.gov*

**Re: Comments on Draft Guidance for Industry #187A, “Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach” (Docket No. FDA-2008-D-0394) and Draft Guidance for Industry #187B, “Heritable Intentional Genomic Alterations in Animals: The Approval Process” (Docket No. FDA-2019-D-2648)**

To Whom It May Concern:

The Animal Welfare Institute (AWI) and the Food Animal Concerns Trust (FACT) appreciate the opportunity to submit the following comments on the Food and Drug Administration’s (FDA) guidance for industry (GFI) #187A Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach<sup>1</sup> and draft guidance for industry (GFI) #187B, entitled “Heritable Intentional Genomic Alterations in Animals: The Approval Process.”<sup>2</sup> AWI was founded in 1951 as a nonprofit organization dedicated to reducing animal suffering caused by people and improving the welfare of animals, including in agriculture, in research, in commerce, at home and in the wild. FACT is a nonprofit organization that works to create a world where all food-producing animals are raised in a humane and healthy manner. We accomplish this by supporting humane farmers, promoting policies that make foods from animals safe and healthy to eat, and helping consumers make informed food choices.

AWI and FACT support FDA’s regulatory authority over intentional genomic alterations (IGAs) in animals. However, we are concerned that animal welfare and ethical analysis are neglected in both GFI #187B and its companion document GFI #187A, which describes the FDA’s “risk-based approach” to regulating IGAs in animals. The FDA’s approach fails to consider or meaningfully address sociopolitical impacts of IGAs, and its measures to assess impacts on the health and welfare of both target and nontarget animals are vague and insufficient.

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<sup>1</sup> U.S. Department of Health and Human Services, FDA, Center for Veterinary Medicine, GFI #187A, Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach (May 2024).

<sup>2</sup> See 89 Fed. Reg. 35,834 (May 2, 2024).

The FDA has developed three categories of IGAs in animals, and it does not require applications from the developer for the first two. Category 1 includes IGAs in animals of nonfood-producing species that are either regulated by other Federal government agencies or entities or raised and used in contained laboratory conditions for research. Category 2 involves IGAs for which FDA believes risks are adequately understood and mitigated and doesn't require an application to be submitted, while Category 3 designates IGAs for which the FDA requires an application for pre-market approval.<sup>3</sup> Specifically, in regard to Category 2, the FDA does not expect developers to submit applications “for approval to market IGAs in food animals that are equivalent to genomic sequences that are found in animals of the same species... with a history of safe use in animal agriculture food production.”<sup>4</sup> Category 2 also includes IGAs in animals raised for food production where the IGAs are “theoretically achievable through conventional breeding and don't result in a change in food.”<sup>5</sup>

The minimal oversight of IGAs designated as “Category 2” is concerning because problems may arise even when an IGA is intended to result only in genomic sequences that could have arisen through conventional breeding or are considered to be equivalent to genomic sequences with a history of “safe use.” For example, in 2020, scientists for the FDA Center for Veterinary Medicine (CVM) published a paper describing unintended alterations produced by genome-editing technology.<sup>6</sup> In it, they describe how producing an IGA for polledness (hornlessness) in cattle resulted in the unintentional – and initially undetected – integration of genetic material from the plasmid used to introduce the polled allele. This genetic material included multiple genes for antibiotic resistance, as well as other genes of bacterial origin, and there is debate as to whether such an error could increase the risk of animals containing the IGA contributing to the global problem of antibiotic resistance.<sup>7</sup> Without the scrutiny of CVM researchers, this would have gone undetected; yet, according to the new guidance, it is not clear that this type of issue, or similar unintended effects, would reliably be identified prior to commercialization.

Moreover, the broad exemptions from applications for IGAs that meet the criteria for being considered “Category 2” IGAs appear to provide blanket approval for many IGAs that could result in significant animal welfare harms. For example, there appears to be interest in using IGA to produce a “double-musced” phenotype,<sup>8</sup> which in some species can also result from conventional breeding and thus would likely not be required to have an approved application. Yet, we know that double-muscling contributes to a host of health and welfare problems, including respiratory disease, difficulty handling heat stress, lameness, dystocia, and muscle

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<sup>3</sup> U.S. Department of Health and Human Services, FDA, Center for Veterinary Medicine, GFI #187A, Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach [pg. 5-10] (May 2024).

<sup>4</sup> U.S. Department of Health and Human Services, FDA, Center for Veterinary Medicine, GFI #187A, Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach [pg. 6-7] (May 2024).

<sup>5</sup> U.S. Department of Health and Human Services, FDA, Center for Veterinary Medicine, GFI #187A, Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach [pg. 7] (May 2024).

<sup>6</sup> Norris, A. L., Lee, S. S., Greenlees, K. J., Tadesse, D. A., Miller, M. F., & Lombardi, H. A. (2020). Template plasmid integration in germline genome-edited cattle. *Nature biotechnology*, 38(2), 163–164. <https://doi.org/10.1038/s41587-019-0394-6>

<sup>7</sup> Trott, J. F., Young, A. E., McNabb, B. R., Yang, X., Bishop, T. F., & Van Eenennaam, A. L. (2022). Animal Health and Food Safety Analyses of Six Offspring of a Genome-Edited Hornless Bull. *GEN Biotechnology*, 1(2), 192–206. <https://doi.org/10.1089/genbio.2022.0008>

<sup>8</sup> Wu, G., & Bazer, F. W. (2019). Application of new biotechnologies for improvements in swine nutrition and pork production. *Journal of animal science and biotechnology*, 10, 28. <https://doi.org/10.1186/s40104-019-0337-6>

degeneration.<sup>9</sup> Because such health problems may turn up in only some of the animals with the IGA, the low numbers of animals used to assess safety for the FDA's review may not be sufficient for reliable detection.

A recent journal article describing the FDA's approval process for PRLR-SLICK cattle indicates that, for Category 2 IGAs, the FDA bases conclusions about the potential harm an IGA may do to a target animal based on data from an extremely low number of animals (two, in this instance), which is insufficient to detect harmful effects that do not occur universally.<sup>10</sup> As the article describes, assessing safety on only a very small number of animals with IGAs makes it difficult if not impossible to identify IGA impacts on health and welfare that results from pleiotropy, or the effect of an IGA on phenotypic traits unrelated to the trait that is being intentionally modified.

The FDA describes means by which it "might" evaluate animal safety to determine if an IGA would fit within Category 2 by identifying "potential changes in an animal's physiology or behavior that interfere with its basic functioning or cause suffering or a potential for elevated susceptibility to disease."<sup>11</sup> However, neither #187B nor #187A lays out a robust framework for incorporating animal welfare considerations. For example, if an IGA increases the probability of developing a particular disease, how can the small number of animals examined be sufficient to detect this? How is "disease" defined? Would this include an increase in the risk of developing liver abscesses resulting from an IGA for higher productivity that results in producers feeding a diet higher in grains? How is "suffering" defined? And what sorts of changes to physiology and behavior would be evaluated? When studying low numbers of individual animals who would typically live in a herd, identifying changes in many behaviors, especially social ones such as aggression or maternal characteristics, would seem nearly impossible.

GFI #187A and #187B could be improved by incorporating a framework for assessing potential animal welfare impacts of IGAs, both when determining whether an application is required and when considering approval for a Category 3 IGA. For example, FDA approval of a Category 3 IGA, or determination that a given IGA qualifies as Category 2, could be made contingent on assessment of the potential of IGAs to result in target animals experiencing negative affective states, such as chronic hunger, pain, discomfort, anxiety, frustration, and debility.<sup>12</sup> Rather than evaluating only the potential for susceptibility to disease, the requirement should be broadened to include considerations of negative health outcomes more generally. The FDA could also require

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<sup>9</sup> Fiems L. O. (2012). Double Muscling in Cattle: Genes, Husbandry, Carcasses and Meat. *Animals: an open access journal from MDPI*, 2(3), 472–506. <https://doi.org/10.3390/ani2030472>

<sup>10</sup> Pozzebon, M., Guldbrandtsen, B., & Sandøe, P. (2024). Gene Editing Cattle for Enhancing Heat Tolerance: A Welfare Review of the "PRLR-SLICK Cattle" Case. *Nanoethics*, 18(2), 6-. <https://doi.org/10.1007/s11569-024-00455-8>

<sup>11</sup> U.S. Department of Health and Human Services, FDA, Center for Veterinary Medicine, GFI #187A, Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach [pg. 6] (May 2024).

<sup>12</sup> Mellor D. J. (2016). Updating Animal Welfare Thinking: Moving beyond the "Five Freedoms" towards "A Life Worth Living". *Animals: an open access journal from MDPI*, 6(3), 21. <https://doi.org/10.3390/ani6030021>; Mellor D. J. (2016). Moving beyond the "Five Freedoms" by Updating the "Five Provisions" and Introducing Aligned "Animal Welfare Aims". *Animals: an open access journal from MDPI*, 6(10), 59. <https://doi.org/10.3390/ani6100059>

that behavior be assessed within the physical and social environment in which animals with IGAs would typically be reared.

In addition, it is important that, before an IGA is permitted to be marketed, the likely impact of commercialization of animals with the IGA be evaluated. These could be classified as both pragmatic and sociopolitical considerations.<sup>13</sup> For example, will IGA-containing animals, due to improved survivability or disease resistance, be kept in commercial conditions with poorer hygiene, higher stocking densities, or more extreme temperatures? As discussed in the paper on PRLR-SLICK cattle mentioned above, such an outcome would potentially negate the animal welfare benefit touted as the motivation behind many proposed IGAs.<sup>14</sup> The widespread use of IGAs in animal agriculture may have negative impacts on small/independent farmers or those in lower-income countries, who may not be able to compete with larger producers utilizing animals with IGAs. While the FDA doesn't consider such sociopolitical considerations when approving drugs, the agency is developing an alternative approval process for IGAs and bioethicists have consistently pointed out the need for such considerations.<sup>15</sup>

In addition to these high-level considerations, AWI and FACT recommend the following modifications to GFI #187B:

1. On page 5, shipment of animals is addressed. It is well documented that very long journeys are harmful to animal health and welfare, particularly when animals are deprived of food and water, as is typical for animals used in food production. Animals with IGAs, particularly those that are still under development, may be more vulnerable to such harms, and transport may complicate evaluation of the animal safety of an IGA. Thus, it should be mandated that fitness for transport be assessed prior to shipping and that transport conditions and duration adequately protect animal health and welfare.
2. On page 6, disposition of animals who are no longer needed for IGA research is discussed. Currently, the recommendation is to euthanize such animals or maintain them in a contained environment. We encourage the FDA to make clear that the "contained environment" may include a private home or accredited animal sanctuary, if appropriate.

Given the potential implications of IGAs on the welfare of individual animals and animal agriculture more broadly, it is imperative that the FDA adopt a more comprehensive framework for regulating IGAs in animals, particularly those used for food production. Bioethicists have

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<sup>13</sup> Almeida, M., & Ranisch, R. (2022). Beyond safety: mapping the ethical debate on heritable genome editing interventions. *Humanities & Social Sciences Communications*, 9(1), 1–14. <https://doi.org/10.1057/s41599-022-01147-y>

<sup>14</sup> Pozzebon, M., Guldbrandsen, B., & Sandøe, P. (2024). Gene Editing Cattle for Enhancing Heat Tolerance: A Welfare Review of the "PRLR-SLICK Cattle" Case. *Nanoethics*, 18(2), 6-. <https://doi.org/10.1007/s11569-024-00455-8>

<sup>15</sup> Almeida, M., & Ranisch, R. (2022). Beyond safety: mapping the ethical debate on heritable genome editing interventions. *Humanities & Social Sciences Communications*, 9(1), 1–14. <https://doi.org/10.1057/s41599-022-01147-y>; Shriver A. (2020). Prioritizing the protection of welfare in gene-edited livestock. *Animal frontiers: the review magazine of animal agriculture*, 10(1), 39–44. <https://doi.org/10.1093/af/vfz053>; Lassen, J., & Jamison, A. (2006). Genetic Technologies Meet the Public: The Discourses of Concern. *Science, Technology, & Human Values*, 31(1), 8–28. <https://doi.org/10.1177/0162243905280021>


recommended adopting the “Principle of Conservation of Welfare” when considering whether a specific IGA should be permitted<sup>16</sup>:

*Principle for the Conservation of Welfare: “any animals that are genetically modified through the use of genetic technology, for purposes other than research, should be no worse off, in terms of suffering, than the parent stock was prior to genetic alterations.”*

To enact this principle, AWI and FACT support creation by FDA of a body of independent experts representing various fields of study, including ethics, animal welfare, veterinary medicine, and environmental and consumer protection, to advise the agency and its staff in addressing this extremely complex and consequential issue.

Thank you in advance for your thoughtful consideration of our comments.

Respectfully submitted,



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<sup>16</sup> Shriver A. (2020). Prioritizing the protection of welfare in gene-edited livestock. *Animal frontiers: the review magazine of animal agriculture*, 10(1), 39–44. <https://doi.org/10.1093/af/vfz053>