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Division of Dockets Management (HFA–305)

Food and Drug Administration

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Rockville, MD 20852

Submitted via [www.regulations.gov](http://www.regulations.gov).

**Comments of Consumers Union to the**

**Food and Drug Administration on the Notice of Availability: Regulation of** **Intentionally Altered Genomic DNA in Animals; Draft Guidance for Industry**

**Docket No. FDA 2008-D-0394**

Submitted by

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**Summary**

Consumers Union, the policy and mobilization arm of Consumer Reports,[[1]](#footnote-1) welcomes the opportunity to comment on the Food and Drug Administration’s (FDA) notice of availability of Draft Guidance for Industry on the Regulation of Intentionally Altered Genomic DNA in Animals. While we would prefer that all “animals whose genomes have been altered intentionally” (also known as “genetically engineered animals,” a term we prefer) be required to go through rigorous safety assessments for both human health and environmental impacts, based on legislation specific to genetically engineered animals, we support FDA treating them in the interim as New Animal Drugs, since there is a required safety assessment process associated with new animal drugs. In other words, gene-edited animals should be treated like other genetically engineered animals.

Given the potential for unanticipated effects stemming from the use of gene editing techniques such as the CRISPR-Cas9 system in animals,[[2]](#footnote-2) all gene-edited animals should be required to be analyzed through whole genome sequencing, as well as epigenetic profiling, to detect off-target effects. This should be followed by a battery of “–omics” testing (transcriptomics, metabolomics, proteomics, etc.), as recommended by both Codex Alimentarius[[3]](#footnote-3) and the National Academy of Sciences,[[4]](#footnote-4) and animal testing to determine the potential health impacts of the intended and unintended changes to the animal as a result of the genetic engineering process. In addition, all food products derived from genetically engineered animals should be required to be labeled, so there is transparency for consumers and any post-market unexepected health effects can be identified.

**Detailed comments**

*Draft revisions to Guidance for Industry (GFI) #187*

FDA has stated that it is revising Guidance for Industry (GFI) #187, “Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs,” to make clear that developers of animals produced using emerging technologies (e.g., genome editing) would fall under this guidance document. We support this action by FDA, since the use of the term “recombinant DNA constructs” implies that genetic material from different sources has been inserted into the genetically engineered (GE) animals. With the use of emerging technologies such as genome editing, inheritable changes in GE animals can be made that do not include genetic material from different sources, and so these animals might not be seen to be covered by GFI #187. We strongly agree with FDA’s language in the Draft Guidance stating that it “addresses animals whose genomes have been intentionally altered using modern molecular technologies, which may include random or target DNA sequence changes including nucleotide insertions, substitutions, or deletions, or other technologies that introduce specific changes to the genome of the animal.”[[5]](#footnote-5) This language is broad enough that it would include the present emerging technologies (e.g., genome editing), as well as future technologies designed to alter the genome of animals.

We disagree with FDA on the notion that “‘altered genomic DNA’ refers to the portion of an animal’s genome that has been intentionally altered ... [and] the altered genomic DNA in an animal is a drug within the meaning of section 201(g) for the FD&C [Food, Drug, and Cosmetic] Act.”[[6]](#footnote-6) We would urge the FDA to use the term “altered genomic DNA” to include *both* intentional and unintentional alterations (e.g., off-target effects) in the animals’ genomic DNA, since FDA has made clear that the genome editing technologies can cause off-target effects and that such information should be supplied to the agency. For example, under the New Animal Drug Application Requirements in the Draft GFI #187, FDA states that under the “Identification” paragraph of the federal rule (21 CFR 514.1(b)(1)), the kind of information that the applicant should provide FDA would include “the name and intended function of the altered genomic DNA, and the number and characterization of the site(s) of *alterations, including unintended (e.g., off-target) alterations, as well* as the intended use of the resulting lineage of animals”[[7]](#footnote-7) *italics* added. The information that would be required under “Manufacturing Methods, Facilities, and Controls” (21 CFR 514.1(b)(5)) should include “full characterization of the site of intentional alterations, any unintended alterations (e.g., off-target alterations, unanticipated insertions, substitutions, or deletions) and … we recommend that you evaluate whether there are any unintended interruptions of a coding or a regulatory region.”[[8]](#footnote-8) FDA clearly is interested in the off-target effects that happen as a result of genome editing. By including the *unintended*, as well as the intended, alterations to genomic DNA in the agency’s definition of “altered genomic DNA”—which FDA considers to be a drug within the meeting of Section 201(g) of the FFD&C Act—the agency would ensure that the applicant includes such data in its application. Thus, **we urge FDA to define “altered genomic DNA” as the portion of the animal’s genome that has been intentionally or unintentionally altered and considered as a drug within the meaning of section 201(g) of the FD&C Act.**

While genome editing has been portrayed in the media as an incredibly precise process, where one can go in and literally only intentionally change one or a small number of nucleotide bases, the reality is that there can be large numbers of off-target effects. There is much interest and research in the use of clustered regulatory interspersed short palindromic repeats (CRISPR) associated systems (e.g., use of CRISPR-Cas9), since such systems are considered to be among the most accurate in making specific changes to an animal’s genome. However, two recent studies show that the level of off-target effects associated with CRISPR-Cas9 is far greater than previously thought, and these effects are not identifiable by the common bioinformatics tools most commonly used to search for unintended effects associated with CRISPR-Cas9.

One study involving two strains of mice that were blind as the result of a mutation in a specific gene and which used a CRISPR-Cas9 system to reverse that mutation so that the mice could see, “found an unexpectedly high number of SNVs [single-nucleotide variants, aka point mutations] compared with the widely accepted assumption that CRISPR causes mostly indels [insertions and deletions] at regions homologous to the sgRNA [single-guide RNA, part of the CRISPR-Cas9 system].”[[9]](#footnote-9) In one strain of mouse there were 1,736 point mutations (SNV) and 164 insertions and deletion mutations, while in a second strain there were 1,696 point mutations and 128 insertion and deletion mutations. Furthermore, these large number of mutations were not in regions that were predicted based on bioinformatics (or *in silico*) models based on similarity to the targeted. In addition, when the genome of the two engineered mouse strains was compared to the 36 mouse strains in the Mouse Genome Project for which full genome sequences have been identified, “[n]one of the CRISPR-generated off-target mutations were found in any of these strains.”[[10]](#footnote-10)

This study raises troubling concerns since it shows that potentially harmful off-target effects, which would not be identified by the current *in silco* methods used, could be far more extensive than previously thought, such that whole genome sequencing (WGS) must be performed to identify all the off-target mutations. As the paper states, “Our results suggest current *in silico* modeling cannot predict bona fide off-target sites. … The unpredictable generation of these variants is of concern. The impact of the numerous mutations occurring in noncoding RNAs or other regulatory intragenic regions could be detrimental to key cellular processes. … The present study demonstrates WGS analysis of both indels and SNVs as the most thorough method for identifying off-target mutations and shows a significantly higher number of potentially deleterious CRISPR-Cas9-induced mutations than have been previously reported.”[[11]](#footnote-11)

A second recently published mouse study, which involved making multiple edits in the mouse genome using a CRISPR/Cas9 system, resulted in large changes including large deletions of up to 600 base pairs, which may not be routinely identified without whole genome sequencing. As the paper noted, “we also obtain large deletions of up to 600 bp …. Our findings also demonstrate that an extended analysis of F1 genotypes is required to obtain conclusive information on the exact molecular consequences of targeting events.”[[12]](#footnote-12)

These two studies clearly show that the CRISPR-Cas9 system is not as accurate as many believe and may result in extensive off-target mutations that might not be detected through the use of simple *in silico* modeling that is widespread. Indeed, to detect all the off-target effects that may be caused by genome editing, **we strongly urge FDA to require whole genome sequencing (WGS) for all gene-edited animals as a way of detecting any off-target mutations.**

One potential way to determine the impact of unintended effects of genetic engineering is through the use of modern molecular and biochemical techniques to look at changes in gene expression, metabolic effects, or changes in proteins, for example, through the so-called “–omics” technologies (e.g., genomics, transcriptomics, proteomics, metabolomics, and epigenomics). As noted in the Codex Alimentarius Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals (CAC/GL 68-2008), “Molecular biological and biochemical techniques can also be used to analyse changes that occur at the level of transcription and translation that could lead to unintended effects.”[[13]](#footnote-13) The National Academy of Sciences 2016 report, *Genetically Engineered Crops: Experiences and Prospects*, also called for the use of –omics technologies to detect unintended effects (although this book refers to GE crops, the same reasoning applies to GE animals).[[14]](#footnote-14) Thus, **we urge FDA to require use of –omics technologies (e.g. genomics, transcriptomics, proteomics, metabolomics, and epigenomics) to detect untintended effects associated with genetic engineering/the new molecular technologies**.

*How to refer to these genome-altered animals*

FDA asks for input on how to refer to animals created using modern molecular techniques. FDA says that for this Guidance, the agency uses the term “animals whose genomes have been altered intentionally,” but that other terms could be “genome-edited animals,” “intentionally altered animals,” or an expanded version of the term “genetically engineered” to include the deliberate modification of the characteristics of an organism by manipulating its genetic material. While FDA’s suggested term is scientifically accurate, the term “genetically engineered animal” may be more understandable to the general public and also makes it clear that the gene-edited animals, or animals produced via other new molecular techniques, are considered to be in the same category as conventionally “genetically engineered animals.”

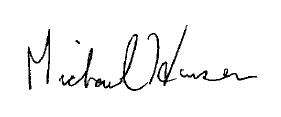
In addition, FDA, in Guidance on Voluntary Labeling from Foods That Have or Have Not Been Derived from Genetically Engineered Plants[[15]](#footnote-15) (similar draft Guidance has been developed for voluntary labeling of foods that have or have not been derived from GE salmon[[16]](#footnote-16)) has stated that the term “genetically engineered” is a synonym for “modern biotechnology,” which is the globally agreed upon language used by Codex Alimentarius. Codex Alimentarius is the food safety standards organization of the United Nations, and is jointly run by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). From 2000 to 2008, there were two rounds of the Codex Alimentarius Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology. This Task Force developed a number of documents, including a Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45, 2003); a Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals (CAC/GL 68, 2008), and separate guidelines for GE microorganisms, as well. The World Trade Organization (WTO) considers that, in terms of food safety, the standards or guidelines of Codex Alimentarius are deemed the global science-based standard and, thus, immune to trade challenges—in other words, they are not considered to be a “non-tariff trade barrier.”

The only term we suggest should not be used is “intentionally altered animals,” as that term is too vague and could also be used to describe animals created via conventional methods of breeding or those created using assisted reproductive technologies.

**We urge FDA to use the term “genetically engineered animals” to refer to animals produced via gene-editing or other modern molecular techniques.**

# Thank you for your consideration of our comments.

Respectfully submitted,



Michael Hansen, Ph.D.

Senior Scientist

# Consumers Union

1. Consumers Union is the policy and mobilization arm of Consumer Reports, an independent, nonprofit organization that works side by side with consumers to create a fairer, safer, and healthier world. As the world’s largest independent product-testing organization, Consumer Reports uses its more than 50 labs, auto test center, and survey research center to rate thousands of products and services annually. Founded in 1936, Consumer Reports has over 7 million subscribers to its magazine, website, and other publications. [↑](#footnote-ref-1)
2. Schaefer KA, W W-H, Colgan DF, Tsang SH, Bassuk AG and VB Mahajan. 2017. Unexpected mutations after CRISPR-Cas9 editing *in vivo*.  *Nature Methods,* (14, 6): 547, 548. <https://www.nature.com/nmeth/journal/v14/n6/full/nmeth.4293.html>; and Shin HY, Wang C, Lee HK, Yoo KH, Zeng X, Kuhns T, Yang CM, Mohr T, Liu C and L Hennighausen. 2017. CRISPR/Cas9 targeting events cause complex deletions and insertions at 17 sites in the mouse genome. *Nature Communications*, 8:15464.At: <https://www.nature.com/articles/ncomms15464.pdf> . [↑](#footnote-ref-2)
3. See Codex Alimentarius 2008. Guideline For The Conduct Of Food Safety Assessment Of Foods Derived From Recombinant-DNA Animals. CAC/GL *68-2008*. Available at: [www.fao.org/fao-who-codexalimentarius/standards/list-of-standards/en/](http://www.fao.org/fao-who-codexalimentarius/standards/list-of-standards/en/). [↑](#footnote-ref-3)
4. National Academies of Sciences, Engineering, and Medicine. 2016. Genetically Engineered Crops: Experiences and Prospects. National Academy Press, Washington, D.C. Available at: <https://www.nap.edu/catalog/23395/genetically-engineered-crops-experiences-and-prospects> [↑](#footnote-ref-4)
5. P. 3 in FDA, 2017. Draft Guidance for Industry #187 Regulation of Intentionally Altered Genomic DNA in Animals, online at: [www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf](http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf). [↑](#footnote-ref-5)
6. P. 7 in *Ibid.* [↑](#footnote-ref-6)
7. Pg. 15 in *Ibid.* [↑](#footnote-ref-7)
8. Pp. 17-18 in *Ibid.* [↑](#footnote-ref-8)
9. Schaefer et al. 2017. *Op cit* [↑](#footnote-ref-9)
10. Pg. 547 in *Ibid.* [↑](#footnote-ref-10)
11. *Ibid.* [↑](#footnote-ref-11)
12. Shin et al. 2017. *Op cit* [↑](#footnote-ref-12)
13. Pg. 3 in Codex Alimentarius. 2008. Guideline For The Conduct Of Food Safety Assessment Of Foods Derived From Recombinant-DNA Animals. CAC/GL *68-2008*. Available at: [www.fao.org/fao-who-codexalimentarius/standards/list-of-standards/en/](http://www.fao.org/fao-who-codexalimentarius/standards/list-of-standards/en/). [↑](#footnote-ref-13)
14. National Academies of Sciences, Engineering, and Medicine. 2016. *Op cit*. [↑](#footnote-ref-14)
15. FDA. 2015. Guidance on Voluntary Labeling from Foods That Have or Have Not Been Derived from Genetically Engineered Plants. At: <https://www.fda.gov/Food/GuidanceRegulation/GuidancedocumentsRegulatoryInformation/LabelingNutrition/ucm059098.htm> [↑](#footnote-ref-15)
16. # FDA. 2015. Draft Guidance for Industry: Voluntary Labeling Indicating Whether Food Has or Has Not Been Derived From Genetically Engineered Atlantic Salmon. At: <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm469802.htm>

    [↑](#footnote-ref-16)