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Public Interest Comment¹ on

The Food and Drug Administration's Draft Guidance for Industry #187
"Regulation of Intentionally Altered Genomic DNA in Animals"

How to Regulate Genome Edited Animals? A Comment on FDA's Proposed Guidance

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The George Washington University Regulatory Studies Center improves regulatory policy through research, education, and outreach. As part of its mission, the Center conducts careful and independent analyses to assess regulatory proposals from the perspective of the public interest. This comment on the Food and Drug Administration's draft guidance does not represent the views of any particular affected party or special interest, but is designed to evaluate the effect of FDA's draft on overall consumer welfare.

Summary

The FDA has proposed an approach to oversight of genome edited animals that closely follows its current policy regarding genetically engineered animals. Unfortunately, the proposed approach is unwise because the existing policy regarding genetically engineered animals, which

¹ This comment reflects the views of the authors, and does not represent an official position of the GW Regulatory Studies Center or the George Washington University. The Center's policy on research integrity is available at <http://regulatorystudies.columbian.gwu.edu/policy-research-integrity>.

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it mimics, has itself simply failed. We recommend that FDA conduct an analysis of the benefits and costs of its proposed review of genome edited animals, and develop any mandatory policy regarding regulation of genome edited animals based on the results of such analysis. In addition, FDA should withdraw its draft guidance for genome edited animals and explore publicly the feasibility and practicality of alternative approaches modeled on its existing program overseeing genetically engineered plants. Finally, FDA should participate, along with other federal agencies including EPA, in the development of standards to identify new organisms that pose significant risk and to protect the environment from the release of such organisms, including animals and plants altered with gene drives.

Introduction

At the end of the Obama Administration, three federal agencies solicited comment on proposed policies to oversee the use of new genome editing techniques—including CRISPR³—to develop new varieties of plants, algae, and animals. These proposals,⁴ issued by the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the USDA’s Animal and Plant Health Inspection Service (APHIS), have set the stage for a decision by the Trump Administration about whether and how to apply the 1986 Coordinated Framework for Biotech Regulation to newer genome editing technologies. These technologies differ from earlier genetic engineering (GE)—recombinant DNA technology—by depending on edits to an existing genome rather than on the insertion of genetic material taken from organisms belonging to another species or even kingdom. The products of genome editing thus might, in principle, occur naturally, an observation that raises questions about risk, and the proper degree of federal oversight, particularly in the absence of legislation specifically addressing these technologies.

On January 19, 2017, FDA proposed to regulate all genome edited⁵ animals under its new animal drug authorities (FDA, 2017c).⁶ More specifically, FDA proposed a finding that altered genomic DNA from modern genome editing in an animal is a drug within 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. The proposed guidance closely follows the existing guidance finalized on January 15, 2009 for genetically engineered animals, but greatly expands the scope of the guidance to cover not only genetically engineered animals but also all genome edited animals. The final 2009 guidance imposed compliance responsibilities on developers of new

³ CRISPR stands for clustered regularly interspaced short palindromic repeats and are segments of DNA that form the basis for a genome editing technology.

⁴ See EPA (2016), FDA (2017c, 2017d, 2017e), USDA APHIS (2017b).

⁵ Note that the abbreviation “GE” is used only for genetic engineering, and not for genome editing, the newer technology. Genetic engineering includes recombinant DNA techniques.

⁶ A narrow exception is genome edited mosquitos for which the innovators make claims limited to pest control and not human or animal health—FDA’s guidance says that EPA would regulate such products as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FDA, 2017d).

animals containing recombinant DNA constructs, i.e., insertion of DNA from another species or even kingdom (FDA, 2009). The guidance FDA proposed in January, 2017 classifies any edits to an animal's genome as a drug, even if the resulting gene sequences already exist in the animal species' own genepool.

Here we explore FDA's regulatory approach and its implications for safety to humans, animals and ecosystems, and for innovation. We conclude that a regulatory approach less stringent than proposed by FDA would be more consistent with longstanding regulatory principles as well as other federal policies. We recommend that

- FDA estimate the benefits and costs of any new mandatory premarket review requirements, as required by longstanding executive orders;
- FDA withdraw its draft guidance 187 and explore publicly a voluntary approach modeled on FDA's review of new genetically engineered plants;⁷
- FDA, along with other agencies including EPA, work to develop standards to identify new organisms that pose significant risk and to protect the environment from the release of such organisms.

Background

Recombinant DNA (rDNA) techniques, which prompted development of the federal Coordinated Framework for Regulation of Biotechnology (Office of Science and Technology Policy, 1986), have been used to develop a large and growing set of products with impressive potential to help solve problems in agriculture, public health and the environment. For example, FDA has concluded review, essentially approving of commercial use of 176 different food crops engineered to have desirable traits such as improved resistance to pests, insects, blight and viruses, changes in composition to improve digestibility of animal feed, herbicide tolerance and improved fertility (FDA, 2017a).

A variety of well-respected scientific and health organizations have reviewed available studies addressing possible human health effects from consumption of genetically engineered food and reached similar conclusions of safety. The Board of Directors of the American Association for the Advancement of Science summarized these conclusions by saying "consuming foods containing ingredients derived from [genetically modified] crops is no riskier than consuming the same foods containing ingredients from crop plants modified by conventional plant improvement techniques" (AAAS Board of Directors, 2012). This is not to say that adoption of such new crops has been trouble-free. Herbicide-resistant weeds have become more common following the

⁷ Note that if FDA continues to pursue this proposed policy, the final guidance document would be subject to President Trump's Executive Order 13771, which would require FDA to remove two existing regulations and offset new costs (President Trump, 2017).

introduction of crop varieties that tolerate herbicides (especially glyphosate) (Duke and Powles, 2009).

Far fewer genetically engineered animals have made it to market. FDA has approved “farmaceutical” animals—a goat, rabbit and chicken that produce therapeutic pharmaceutical products for use in humans (Heavey, 2009; Becker, 2015), but FDA has approved for human consumption only one product, AquaBounty’s fast-growing AquaAdvantage salmon (FDA, 2015). No other genetically engineered animals with the potential to benefit humans and or animals have been approved for commercial use and there is limited progress toward approval of potentially important genetically engineered products. FDA has issued a final environmental assessment with a finding of no significant impact for release of a genetically engineered version of *Aedes aegypti* developed by Oxitec, a British firm, to control populations of mosquitos that carry dengue and Zika virus (FDA, 2016). This decision may lead to field trials, if local authorities consent, but does not constitute approval for commercial sale. Researchers at the Roslin Institute of Edinburgh University have developed a genetically engineered chicken that does not transmit avian influenza to other birds. They believe that this genetic modification “has the potential to stop bird flu outbreaks spreading within poultry flocks.” In addition, it would “not only protect the health of domestic poultry but could also reduce the risk of bird flu epidemics leading to new flu virus epidemics in the human population” (Roslin Institute, 2017). We are unaware of any information indicating this product has been submitted for review to FDA or comparable agencies in the EU.

The advent of CRISPR has led researchers to launch a variety of innovative projects. Some involve resurrecting lost species, such as the mammoth and the passenger pigeon, or protecting extremely endangered species, such as the endemic Hawaiian birds threatened by invasive avian malaria (NAS, 2016). Some involve increasing agricultural productivity, e.g., through hornless dairy cattle (Carlson et al., 2016), and “double-muscled” goats (Yu et al., 2016). Others involve projects to control human disease dependent on wild animal hosts, such as Lyme disease, schistosomiasis, and even malaria (NAS, 2016), which still kills some 420,000 people annually (WHO, 2016).

Some of these projects involve so-called gene-drives—modifications designed to quickly spread certain traits throughout wild populations. Gantz et al. (2015) used a CRISPR gene-drive to modify *Anopheles stephensi*—a mosquito that carries malaria—to spread malaria resistant genes throughout a population, even when one parent is the wild-type. Gene-drive modified organisms could in principle be used either for population suppression or population replacement (NAS, 2016). Gene-drive products to date have been limited to yeast and insects, with preliminary progress reported for mice (Regalado, 2017). Some recent research raises questions about the stability and durability of the effects of gene-drive modified organisms (NAS, 2016). The extraordinary and growing set of potentially transformational solutions to both new environmental problems and age-old afflictions demands careful consideration of the

institutional and regulatory mechanisms to ensure that such solutions are appropriately encouraged, while also limiting the risks of unintended human or ecological impacts.⁸

Regulatory Context

The FDA's 2017 Draft Guidance states (p. 7):

For purposes of this guidance, “altered genomic DNA” refers to the portion of an animal’s genome that has been intentionally altered. Unless otherwise excluded, e.g., certain mosquito-related products, the altered genomic DNA in an animal is a drug within 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 the diagnosis, cure, mitigation, treatment, or prevention of disease in the animal. Altered genomic DNA may result from random or targeted DNA sequence changes including nucleotide insertions, substitutions, or deletions, or other technologies that introduce specific changes to the genome of the animal.⁹

A decision to view intentional alterations to genomic DNA as a drug in the meaning of section 201(g) implies that all such animals will be subject to mandatory premarket review and approval, and that they and all progeny will be subject to oversight as new animal drugs. We make three observations about the scope of this decision.

1. Although presented as a guidance and not federal regulation, this document should properly be read as imposing regulatory requirements on regulated entities. A standard FDA template, which appears on FDA Guidance 187 and all other FDA guidance documents, states the guidance “does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the

⁸ We chose not to address risks associated with malevolent use of genome editing techniques, e.g., by rogue states for bio-warfare purposes or for bioterrorism (e.g., Porterfield, 2016). Such risks may be large, insofar as synthetic biology may now allow researchers with well-equipped labs to recreate smallpox, as well as the modification and possible weaponization of sundry microbes. We note, however, that authoritative public health recommendations to the World Health Organization (WHO) regarding public health implications of synthetic biology related to smallpox do not include restrictions on the use of synthetic biology, presumably because the technology is globally available and not subject to conventional domestic regulatory oversight in industrialized democracies such as the U.S. Instead the recommendations cover early detection and diagnostics, increased capacity for disease control, increased biosecurity, and more effective risk communication (World Health Organization, 2015).

⁹ Section 201(g)(1) states: The term “drug” means [(A)...;](B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.”

Notwithstanding this template, no entity interested in developing genome edited animals is likely to seek alternative approaches to comply with the requirements of the applicable statutes and regulations. In addition, entities seeking to develop new breeds of animals through CRISPR or other gene editing technologies are unlikely to contest this guidance in court and should be expected to comply, because of the regulatory power of FDA to take enforcement action against non-compliant entities, as well as deference that FDA receives in court.

2. It departs sharply from the thrust of the 1987 Coordinated Framework for the Regulation of Biotech, which sought to regulate the products derived from biotechnology on the basis of the risks they might pose rather than the method of their creation. This guidance, to the contrary, takes aim at “modern molecular technologies,” explicitly excluding random mutagenesis followed by phenotypic selection. A footnote states “The term “modern molecular technologies does not include selective breeding or other assisted reproductive technologies, including random mutagenesis followed by phenotypic selection.” But random mutagenesis followed by phenotypic selection (though to our knowledge rarely if ever used in animal breeding), would generally result in more rather than less random genome alterations than the targeted modern technologies that this guidance would regulate.

FDA also acknowledges that the new genome editing technologies “are intended to introduce alterations at specific sites in the genome, rather than the more random changes associated with rDNA technology” (FDA 2017c). FDA’s approach thus may be seen as imposing more stringent regulatory requirements on technologies expected to result in less random phenotypic outcomes and therefore generally expected to entail less risk of unintended changes to the genome. In addition, the “altered genomic DNA” produced by “modern molecular technologies” that FDA’s draft guidance asserts is a drug within the meaning of section 201(g) of the FD&C Act, is not objectively identifiable. In many instances the exact same alteration could result from conventional breeding practices.

Put differently, since genome editing in many cases would simply allow faster development of animal breeds that might instead result from conventional animal breeding, in these cases there would be no objective scientific method to distinguish between regulated products (those animals developed through use of genome editing), and unregulated products (those animals that result from conventional animal breeding methods). These animals would be identical except for the method used to create them, which may have been used several generations earlier. In such cases, FDA’s proposed

guidance would regulate differently based solely on the method used to develop the new breed or strain.

3. The regulatory requirements associated with this guidance are substantial. For example, the guidance lists requirements that apply before approval to market (shipping and labeling, animal disposition, use of research animals for animal feed, and environmental considerations). Approval for marketing requires compliance with FDA's new animal drug regulatory requirements (including information to describe the source, identity, purity and functionality of the genome editing). Post-approval responsibilities involve drug registration and listing, recordkeeping, annual reports and supplements to an approved application, as well as records and reports concerning experience with an approved product. Compliance with these regulatory requirements comes only with substantial additional cost in the development, approval and post-marketing surveillance of genome edited animals.

These observations suggest that the proposed guidance is a substantial departure from pre-existing federal policy towards biotechnology regulation and that it is inconsistent with longstanding policies regarding federal regulation. For example, President Clinton's Executive Order 12866, which has been in effect since 1993, states that agencies should propose or adopt regulations "only upon a reasoned determination that the benefits of the intended regulation justify its costs" (President Clinton, 1993). FDA's draft guidance, which has the effect of a regulation, contains no evidence of such a reasoned determination, and would appear to be incompatible with it.

In particular, FDA discusses risks in its draft guidance but makes no argument that any potential risk reduction that might result from compliance with its revised Guidance 187 in some way justifies its costs. In addition, there is no economic analysis of the benefits and costs of the guidance, although Executive Order 12866 requires such analysis of economically significant regulations. Such an analysis would involve estimating the negative effect that this level of regulatory oversight might have on the development, marketing and use of genome edited animals to help address various problems in agriculture, environmental protection, nutrition, and health.

The chilling effect of a complex and burdensome regulatory process may be substantial. Since FDA issued the original Guidance 187 in 2009, the agency has approved exactly one product for food use, AquaBounty's fast-growing AquaAdvantage salmon, and no products other than the previously mentioned pharmaceutical animals. This record suggests that continuing FDA's approach to genome edited products, which may generally be expected to entail less risk of unintended changes to the genome than genetic engineering, may deter development of products that might benefit people and/or animals. At issue, then, is how to formulate an alternative

regulatory approach that allows for the realization of these benefits while limiting genuine risks, all within the FDA’s existing statutory authority.

Comparison with Other Federal Policies

The excessive stringency of FDA’s approach to regulate genome edited animals is seen more clearly by contrasting it with the FDA’s approach to genetically engineered and genome edited plants (FDA, 2017a, Landa, 2015). FDA’s approach to genetic engineering of plants has been voluntary for roughly two decades and largely successful, in that use of GE plants has increased while concerns over safety have abated (with the exception of effects of herbicide tolerant varieties and the associated herbicides on the prevalence of superweeds). FDA has solicited comments regarding its oversight of genome edited plant varieties, but without issuing a proposed guidance (FDA 2017e).

Comparisons with other federal policies are more complicated, in part because the full set of federal regulatory policies is a complex mosaic of agencies, authorizing statutes and innovative products, as illustrated in Table 1.

Table 1: Federal Regulation of Various Products Developed with Biotechnology		
Agency	Statute	Selected Products
EPA	Federal Insecticide, Fungicide and Rodenticide Act	Plant-incorporated protectorants
		Genetically engineered microbial pesticides i.e., bacteria, fungi, viruses, protozoa, or algae
	Toxic Substances Control Act	New chemical substances (not otherwise regulated), including genetically engineered microbes
FDA	Federal Food Drug and Cosmetics Act	Genetically engineered plants that do not incorporate pesticides, do not have plant incorporated protectants, and do not pose risks to crops (This program is voluntary.)
		Genetically engineered animals
USDA / APHIS	Plant Protection Act	Genetically engineered or genome edited organisms that may pose a risk to plant health
Notes: The National Environmental Policy Act (NEPA) also applies to EPA, FDA and USDA/APHIS decisions.		

There are no a priori reasons that genome edited animals merit more stringent regulatory oversight than plants, other than concerns for animal welfare, as discussed below. Both plants and animals can be consumed as food and cause allergic reactions and/or food-borne illnesses. Both plants and animals have major impacts on ecosystems through their interactions with other species and abiotic factors. Both plants and animals can reproduce sexually, causing only half of their genes to be passed on to their offspring. Sexual reproduction is a process of creating

individuals with novel combinations of alleles. FDA Guidance 187 proposes to regulate animals much more stringently than plants without any demonstration of a greater health risk or ecological risk to merit the different regulatory approach. It also proposes to regulate forms of genome editing that result in less novel genomes than occur naturally through sexual reproduction.

Discussion

FDA's proposed approach to genome edited animals is more stringent than other federal regulatory approaches and the greater stringency is not motivated by any clearly identified concern with risk. We explore here whether it might be motivated by characteristics of animals that are unique among living organisms, such as their ability to sense pain. Under the FDA's proposed guidance for genome edited animals, FDA would approve new genome edited breeds as new animal drugs, i.e., only after assessing benefits to the animal and risks and making a determination that the benefits outweigh the risks. (FDA, 2017b). Thus, categorizing edited genes in animals as drugs actual gives new breeds a measure of protection from intrinsically harmful innovations.

It would seem to be worthwhile, however to put this measure of protection in perspective. First, while there exist some federal protections for animal welfare, these are limited. The Animal Welfare Act (AWA) stipulates that facilities using regulated animals for regulated purposes must provide their animals with adequate housing, sanitation, nutrition, water and veterinary care, and they must protect their animals from extreme weather and temperatures (USDA, 2017). Many animals, however, are not covered: "farm animals used for food or fiber (fur, hide, etc.); coldblooded species (amphibians and reptiles); horses not used for research purposes; fish; invertebrates (crustaceans, insects, etc.); or rats of the genus *Rattus* and mice of the genus *Mus* that are bred for use in research. Birds are covered under the AWA but the regulatory standards have not yet been established" (USDA, 2017). Thus, one question is whether FDA should motivate its regulatory approach for genome edited animals by an interest in giving them greater protection than exists for conventional animals under federal law.

Second, genome editing, like genetic engineering could be used in a manner that would substantially benefits animal welfare. In 2015 an outbreak of bird flu among chicken flocks in the American Midwest led to culling—including through burial and incineration—that eventually destroyed more than 30 million chickens (Lowe and Boden, 2015). The genetically engineered Roslin chicken "has the potential to stop bird flu outbreaks spreading within poultry flocks" (Roslin Institute, 2017). The Roslin Institute adds "Disease resistance is clearly a beneficial characteristic for animal welfare and public health." Other novel products being developed with genome editing, such as to fight avian malaria in Hawaii, may promote animal welfare since they could be used to protect Hawaiian honeycreepers from weakness, loss of appetite, symptoms of depression, and death (NAS 2016, Rogers 2012).

Conclusions

The FDA has proposed an approach to oversight of genome edited animals that closely follows its current policy regarding genetically engineered animals, as embodied in its 2009 Guidance on Regulation of Genetically Engineered Animals. Unfortunately, the proposed approach is unwise because the existing policy regarding genetically engineered animals, which it mimics, has itself simply failed.

In developing the 2009 Guidance, FDA and other federal officials expected that FDA's pre-market review of genetically engineered animals as new animal drugs would promote public confidence in their safety. In addition, they hoped that the establishment of a clear and uncontested path to market would stimulate efforts to develop innovative products that might pass FDA scrutiny and directly promote human and animal health (such as the Oxitec mosquito and the Roslin chicken). They were successful in that the 2009 Guidance was largely accepted by industry and public interest groups as well as the Obama Administration which took office later in 2009.

In other relevant respects, however, the policy failed. Since 2009, FDA has approved only three animals used to produce pharmaceutical products, and exactly one product, AquaBounty's fast growing salmon, for food consumption. Further, it is unlikely that FDA is about to approve other genetically engineered animals. FDA in 2009 announced it would generally seek advice from one of its advisory committees before approving new genetically engineered animals and it has not convened or announce any such meetings. Thus, while scientific progress regarding genetic engineering and genome editing has been breathtaking, the existing FDA regulatory process has functioned as if designed to delay and forestall timely approvals to produce and market new genetically engineered animals.¹⁰

We believe that FDA's proposed guidance for genome edited animals lacks a cogent scientific basis, is inconsistent with FDA's policies regarding genome edited plants, and is unlikely to advance FDA's mission to protect and promote public health. We also believe it is inconsistent with the principles of President Clinton's Executive Order 12866, which has been endorsed by the Trump Administration. We therefore recommend that the agency develop a new policy regarding genome edited animals, based on the following steps:

- First, FDA should conduct an analysis of the benefits and costs of its proposed review of genome edited animals, including the expected reduction in risk, if any, that such review might achieve. Since the Reagan Administration, regulatory agencies have conducted benefit-cost analyses of major regulatory decisions as a matter of course and any

¹⁰ The three animals intended to be used to produce pharmaceutical products are an unimportant exception since these valuable animals are kept in stringently regulated enclosures.

mandatory policy regarding regulation of genome edited animals needs to be developed based on the results of such analysis.

- Second, FDA should withdraw its draft revision to Guidance 187 and explore publicly the feasibility and practicality of alternative approaches modeled on its existing program overseeing genetically engineered plants, as explained by Landa (2015). FDA reports that “Credible evidence has demonstrated that foods from the genetically engineered plant varieties marketed to date are as safe as comparable non-genetically engineered foods,” (FDA, 2017), a view shared by other organizations (e.g., AAAS Board of Directors, 2012). FDA in its proposed guidance for genome edited animals offers no compelling reason why intentionally altered genomic DNA in animals necessarily requires greater regulatory oversight than exists for plants. FDA has not proposed mandatory pre-market review of genome edited plants.
- Finally, because of the possibility of complex and unpredictable ecosystem effects from the unintended release of some genome edited organisms, FDA should participate, along with other federal agencies including EPA, in the development of standards to identify new organisms that pose significant risk and to protect the environment from the release of such organisms, including animals and plants altered with gene drives.

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