A Menagerie of Moral Hazards: Regulating Genetically Modified Animals

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Dairy cattle naturally grow long and dangerous horns. So as a protective measure, farmers permanently remove calves' small horns through a painful procedure. Recently, scientists have used modern genetic editing techniques to create dairy cattle that never develop horns, and so never need to be "dehorned".[1] The regulatory fate of these genetically dehorned cattle may be bound up with numerous more controversial cases from the same rapidly diversifying field: the genetic editing of animals. Or, at least so it could be under draft FDA guidance which closed for public commentary in June 2017. The FDA's challenge is to chart a flexible regulatory course. One which will support the potential of gene-editing technology, while staking out the boundaries of acceptable risks - i.e. the ethical boundaries - of the looming "CRISPR zoo"[2]. Here we review the background to the draft guidance, as well as the scathing comments it received from disparate interest groups. The comments show that to foster public trust in how gene-editing technologies are used, it is imperative that the FDA re-engage with all stakeholders, including the public at large.

In their draft guidance, the FDA proposed to regulate "intentionally altered genomic DNA" of animals as a drug being evaluated for use in animals. The originally altered animal, and all its progeny, would be subject to the animal drug regulations.[3] They put out a call for comments on these proposed amendments. As we discuss here, a mere handful of the 151 comments they received were supportive,[4] and most were extremely critical, including those from the National Association of State Departments of Agriculture (NASDA). We argue that the FDA's proposals as they stand are unsatisfactory and should be withdrawn.

Motivation for the proposals

Humans have been selectively breeding animals, and thereby intentionally altering their genomic DNA, since the dawn of domestication. Mutagenesis (chemical or radiation-based) followed by trait-based selection has been used for plants, and, to some extent, animals, for several decades.[5] The FDA excluded both selective breeding and mutagenesis from its definition of intentionally altered genomic DNA.

Genetic engineering via splicing DNA sequences from one species into another (recombinant DNA techniques, "transgenes") were first demonstrated in the early 1980s.[6] More recently, gene-editing techniques such as CRISPR have been developed.[7] These are designed to introduce edits at precise locations in the genome, compared to, in the FDA's words, "the more random changes associated with genetic engineering".[8] Of these modern technologies, CRISPR in particular is simple and cheap, making barriers to its use very low, with do-it -yourself CRISPR kits aimed at biohackers now available.

Genetically altered animals have been developed or proposed, among other purposes, for research to better understand human health and disease, to improve the food supply, to produce pharmaceuticals, to make pets, to bring back extinct species, to reduce the impact of invasive species, and to control populations that spread disease.

Already developed examples in the food category include the previously mentioned dairy cattle gene-edited to not have horns, salmon that grow much faster than normal due to inclusion of a gene that boosts growth hormone levels,[9] pigs resistant to certain viruses,[10] chickens genetically engineered to not transmit avian flu to other birds,[11] and low-fat pigs, produced through the inclusion of a gene that most other mammals have that allows them to better regulate their body temperature.[12] In the pet category are GloFish, aquarium fish that glow due to the inclusion of fluorescent protein from other species, and micro-pigs.[13] Animals developed for pharmaceuticals include a goat that produces an anticlotting protein in its milk, a chicken whose eggs contain a drug for a specific cholesterol disease, and pigs modified to bring the prospect of pig organs for human transplant one step closer.[14] Combating genetic disease due to in-breeding of purebred pets is a target for gene-editing. For example, almost all Dalmatians have a disease called hyperuricemia, which causes stones that can block the urethra and can lead to a burst bladder. The genetic edit to cure this disease was being pursued by a biohacker.[15] Other animals under development include mice (a vector of Lyme disease) modified to make them immune to Lyme disease,[16] gene drives against invasive rodents,[17] and the de-extinction of species such as the passenger pigeon and wooly mammoth.[18] Of these examples, some are based on the older genetic engineering technology of recombinant DNA, and some are enabled via modern gene-editing techniques.

These examples demonstrate that the underlying genetic change can range from giving more animals healthy alleles that are already existing in that breed (the Dalmatians), to introducing alleles from closely related breeds (the hornless cattle), or from related species (the low-fat pigs). They include the removal of certain genetic elements (the pigs for possible organ donation). And they include the addition of genes from more distantly related species (the GloFish). The possibilities are vast.

Background to the proposals

The history of regulating animal genetic modifications in the United States started in the 1980s in response to the first successful interspecies gene transfers, using recombinant DNA. These successes prompted questions of the regulatory approach to their myriad potential commercial applications. In response, the Reagan administration assigned three agencies for oversight of responsibility - the FDA, the U.S. Department of Agriculture (USDA), and the U.S. Environmental Protection Agency (EPA). The administration set out its vision in the Coordinated Framework for Regulation of Biotechnology in 1986, subsequently updated in 1992 and again in 2017.[19] These new regulatory oversight responsibilities were framed as extensions of the agencies' respective existing powers. The updated Coordinated Framework states that the agencies will only exercise regulatory authority over biotechnology products based on cost-benefit risk analysis, irrespective of the technology used to produce them.

In 2009 the FDA issued guidance #187 aimed at bringing all genetically engineered animals under its review, not only those for consumption or altered to produce pharmaceuticals.[20] An FDA spokesperson explained that the timing was "because commercialization of these animals is no longer 'over the

horizon'."[21] The 2009 guidance justified this expansion of jurisdiction through a novel interpretation of animal drugs in the Federal Food, Drug, and Cosmetics Act of 1938.[22] The definition of an animal drug includes "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." Being regulated as a drug involves requirements that hold during product development, an extensive approval process, and post-approval responsibilities. This would apply to the originally developed animals and all their progeny for perpetuity. The FDA has to date approved just three animals: the goat (2009) and chicken (2015) for pharmaceutical applications, and the fast-growing salmon (2015). They deliberated over the salmon for 20 years, raising concerns about their process.

The regulation of genetically engineered animals can be contrasted with that of plants. Whereas the underlying technologies are the same, and potential consequences on the environment and on human health may be similar, no semblance of this comparability appears in the regulatory framework. The USDA reviews genetically-engineered plant products under the Plant Protection Act, to assess risk to plant health. Once a crop passes USDA review, it may undergo a voluntary review by the FDA. As of December 2017, 178 genetically altered crops had been approved through this process.[23] The USDA regulatory approach was based explicitly around recombinant DNA, and does not extend to gene-editing.[24] This process-based approach, rather than a risk-based approach, has meant that around 30 plants developed using gene-editing techniques in the past five years have bypassed regulatory oversight.[25]

In light of the advent of gene-editing technologies, in July 2015 the Obama administration launched a process to modernize the 2009 guidance on biotechnology regulation. They commissioned a report from the National Academies of Science on the future of biotechnology, focused on risks and how to assess them. They also called for the roles of the different agencies to be clarified, and for a long-term regulatory strategy to be developed.

On January 19 2017, President Obama's last day in office, a flurry of guidance proposals were published. The FDA put forward three proposals: an updated version of guidance #187, extending guidance covering animals genetically engineered with recombinant DNA constructs ("transgenes") to cover gene editing[26]; a proposal ceding regulation of mosquito population levels to the EPA; a proposal that their regulation of genetically edited plants would be no different to genetically engineered plants, which is on a voluntary basis.[27] Meanwhile the USDA made proposals updating their regulation of genetically engineered plants. All proposals were opened for a period of public comment.

In November 2017, after reviewing the comments received from the public, the USDA announced that they were withdrawing their proposed guidance.[28] Instead, they announced they will begin again by re-engaging with stakeholders. The USDA disclosed that they had received 203 comments on the draft guidance including both criticism that the proposed guidance would unduly lengthen the time to market of technologies, as well as that the process was "insufficiently rigorous".

The backlash to the proposals

The 151 comments the FDA received in response to its draft guidance concerning animals represents a snapshot of a broad range of interests and concerns, which we summarize here. The majority (117) of responses came from individuals, 14 from organizations associated with farming, 7 technology companies, and 13 others, including consumer organizations.[29] Fewer than ten were supportive of the FDA's approach. A minority (~20) were neutral. The vast majority (~80%) opposed the proposed guidance.

The most common opposition, in an argument that appeared independently in at least 50 responses, was that the product, and not the process that created it, should be regulated. Most stated further that regulation should be based on the risks that these products pose, and that these should be weighed against benefits. These voices see the proposed guidance as a move away from the coordinated framework. Several commentators referenced the approach suggested in the National Academies' report. The report recommends a risk-based framework taking into account the complexity of the product, and its familiarity compared to existing products (whose risks are assumed to be better understood).[30] Several commentators express concern that the regulations as proposed will stifle needed innovation, and ensure that only the largest biotechnology firms will be able to participate. One of the most damning comments comes from NASDA, who represent the State Departments of Agriculture, co-regulators in this space. They call the proposals a "reversal of policy", lacking risk-based justification, and running counter to the administration's policy of reducing regulation and promoting innovation.

Another repeated concern was that the process-focused approach bolsters anti-science fear mongering. A representative comment stated that the proposed guidance "demeans scientists, misinforms the public about biological sciences, and regulates based on fear and trembling rather than identified risks."[31]

The Centre for Food Science, a public interest and environmental advocacy organization, put together comments that were signed by 23,777 of their members (submitted as a single submission), with a further 12 individuals, the Friends of the Earth (on behalf of their over 1 million members), and the Consumers Union submitting the same or similar comments. They claim that the FDA "does not have authority under its enabling statute to regulate GE animals or insects absent a GE-specific statute passed by Congress", and they call for a moratorium on the approval of all genetically modified animals prior to such legislation. They also place emphasis on understanding the risks posed by these new technologies. A small number of individuals voiced outright opposition to any genetic modification of animals, stressing the unacceptability of the voluntary nature of regulation for genetically engineered plants, and the need for clear labelling of all genetically engineered foods.

A dozen individuals opposed the guidance arguing it severely hinders our ability to help cure genetic disease in animals, as in the Dalmatian example.

Three technology firms working on genetically modifying animals for non-food applications called for separate regulation for non-food products. The National Aquaculture Association and the California Department of Fish and Wildlife wrote with concerns that the guidelines as proposed would inappropriately cover established treatments used to induce desirable chromosomal abnormalities in fish.

Responses from all sides show frustration at the lack of coordination across the different federal agencies. The Centre for Food Science calls for a cohesive interagency framework, NASDA reference “the apparent lack of coordination between FDA and its sister agencies in the Federal government.” The NAS report tactfully states that the existing regulatory approach “could be considered to appear fragmented”.[32]

The proposals should be withdrawn

We agree that it should be the product that is the subject of regulation, and not the process that created it. A focus on product would force the FDA to clarify aspects of their regulatory intent, increasing transparency not just for product developers, but also for the public. It would elevate the importance of understanding risk, a call that was shared by a broad cross section of commenters. By contrast, a focus on process bunches diverse applications under one umbrella, from curing inherited diseases to adding in genes from distant species, from food to de-extinction of animals. And it divides products that should be considered together: The USDA excluded from their proposed regulations any genetically modified organism that could have been produced using traditional breeding techniques, because "[s]uch organisms are essentially identical, despite the method of creation."[33]

Moreover, history has shown that biotech regulations focusing on process have a frustratingly short shelf life. Regulation introduced in 2009 focused on process, calling out recombinant DNA. Just a few years later, new technologies arrived that are not covered by that regulation. Updating guidance with updated technologies repeats the original error. Already technology is outpacing proposals: mice have had their epigenomes successfully edited, and as these terms are currently understood these would not qualify as having “intentionally altered genomic DNA”.[34]

A focus on process has allowed the FDA to avoid answering tough product questions. This needs to change. The approach proposed by the National Academies in their report concerning the future products of biotechnology, in our opinion represents a sound core for a revised approach: a single cross-agency entry point for the risk based appraisal of new products. In the context of technology designed to affect animals, an additional concern should be for animal welfare. Technology such as gene editing has huge potential to not only improve animal welfare, but also to decrease it.

The lack of consistency across different agencies concerning genetically altered organisms is not only confusing within the U.S.: it makes it almost impossible for other countries to follow the U.S.’s lead. The aim should be internal consistency within the U.S. as part of a cohesive international approach for these international issues: protecting us from large-scale risk while helping us provide for the food security and better health of humanity.

Finally, the FDA received a similar number and spread of comments as the USDA received in reaction to their proposals. The same arguments cited by the USDA in withdrawing their own proposals apply equally to the FDA. In both cases, the proposals clearly fail to attract even minimal support from a broad range of commenters. Moreover, as the USDA noted, the publication of the proposed rules constrained their ability to explore alternatives with stakeholders. Their withdrawal opened up the opportunity for “a more open and robust policy dialogue.”[35] Given the opposition against their proposals, it would be

consistent for the FDA to likewise withdraw them, as a first step towards a cohesive framework. Then we can talk about the details of a risk-based approach, both for gene-editing and for the biotechnologies to come.

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[1] Recombinetics (St. Paul, MN, USA) has produced hornless Holstein cows (Carlson et al., 2016). The hornless or 'polled' phenotype results from naturally occurring mutations at the POLLED locus, common in beef breeds but not in dairy breeds

[2] S. Reardon, "Welcome to the CRISPR Zoo," *Nature* 531, no. 7593 (2016): 160, https://www.nature.com/news/welcome-to-the-crispr-zoo-1.19537.

[3] U.S. Food and Drug Administration, Notice, "Regulation of Intentionally Altered Genomic DNA in Animals; Draft Guidance for Industry; Availability," *Federal Register* 82, No. 12, (January 19, 2017): 6561, https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-00839.pdf.

[4] "Regulations.gov - Docket Browser," *Regulations.gov*, accessed December 14, 2017, https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=PS&D=FDA-2008-D-0394. 159 comments were received; 8 were clear duplicates.

[5] *Genetics and Mutagenesis of Fish*, ed. J. H. Schröder (Berlin: Springer-Verlag, 1973).

[6] As reviewed in U.S. Food & Drug Administration, "Guidance for Industry: Regulation of Intentionally Altered Genomic DNA in Animals, Draft Guidance #187," https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf (accessed December 14, 2017).

[7] H. Wang, H. Yang, C.S. Shivalila, M.M. Dawlaty, A.W. Cheng, F. Zhang and R. Jaenisch, "One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering", *Cell*, 153 (2013): 910-18, http://www.ncbi.nlm.nih.gov/pubmed/23643243 (accessed December 14, 2017).

[8] Ibid.

[9] E. Entis, "Aquadvantage Salmon: A Case Study in Transgenic Food," *Animal Biotechnology* 9, no. 3 (1998): 165, doi: 10.1080/10495399809525906.

[10] Genus (Basingstoke, UK) has developed pigs resistant to porcine reproductive and respiratory syndrome virus

[11] Jon Lyall et al., "Suppression of Avian Influenza Transmission in Genetically Modified Chickens," *Science* 331, no. 6014 (2011): 223, http://science.sciencemag.org/content/331/6014/223.

[12] R. Stein, "CRISPR Bacon: Chinese Scientists Create Genetically Modified Low-Fat Pigs," *National Public Radio*, October 23, 2017, https://www.npr.org/sections/thesalt/2017/10/23/559060166/crispr-bacon-chinese-scientists-create-genetically-modified-low-fat-pigs.

[13] D. Cyranoski, "Gene-edited 'micropigs' to be sold as pets at Chinese institute," *Nature* 526, no. 7571 (2015): 18, https://www.nature.com/news/gene-edited-micropigs-to-be-sold-as-pets-at-chinese-institute-1.18448.

[14] K. Fischer et al., "Efficient production of multi-modified pigs for xenotransplantation by 'combineering', genestacking and gene editing," *Scientific Reports* 6:29081 (2016), https://www.nature.com/articles/srep29081.pdf.

[15] A. Rosenblum, "A Biohacker's Plan to Upgrade Dalmatians Ends Up in the Doghouse," *MIT Technology Review*, February 1, 2017, https://www.technologyreview.com/s/603530/a-biohackers-plan-to-upgrade-dalmatians-ends-up-in-the-doghouse/.

[16] C. Goldberg, "One Step Closer To Making Mice That Fight Lyme, Scientists Ask Nantucket: Should We Move Forward?" *WBUR 90.9*, August 17, 2017, http://www.wbur.org/commonhealth/2017/08/17/gene-scientists-nantucket-lyme.

[17] See the work of the Genetic Biocontrol of Invasive Rodents (GBIRd)

[18] Revive & Restore has several de-extinction projects. "Passenger Pigeon Project," *Revive & Restore*, accessed December 14, 2017. http://reviverestore.org/about-the-passenger-pigeon/.

[19] U.S. Environmental Protection Agency, "Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology," https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf (accessed December 14, 2017)

[20] U.S. Food & Drug Administration,*Guidance for Industry: Regulation of genetically Engineered Animals Containing Heritable Recombinant DNA Constructs: Final Guidance*, FDA-2008-D-0394 (Washington DC, 2009), https://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0394-gdl.pdf.

[21] M. Wadman, "FDA to regulate genetically engineered animals," *Nature*, September 19, 2008, http://www.nature.com/news/2008/080919/full/news.2008.1120.html. Quote from Randall Lutter, the FDA's deputy commissioner for policy

[22] *Federal Food, Drug, and Cosmetic Act*, *U.S. Code* 21 (1938), §§ 321 et seq.

[23] U.S. Food & Drug Administration, "Biotechnology Consultations on Food from GE Plant Varieties," https://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon (accessed December 14, 2017).

[24] Agriculture, Regulations of the Department of Agriculture, 7b C.F.R. §340.1 (2017): 455, https://www.gpo.gov/fdsys/pkg/CFR-2017-title7-vol5/pdf/CFR-2017-title7-vol5-sec340-1.pdf.

[25] E. Waltz, "Gene-edited CRISPR mushroom escapes US regulation," *Nature*, April 14, 2016, http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754.

[26] "Draft revised GFI #187 is intended to clarify that, unless otherwise excluded, the altered genomic DNA in an animal (referred to in this document as ''animals with intentionally altered genomic DNA'') that is intended to affect the structure or function of the body of the animal or, in some cases, to diagnose, cure, mitigate, treat, or prevent disease in the animal, meets the drug definition in section 201(g) of the FD&C Act." U.S. Food & Drug Administration, Notice, "Regulation of Intentionally Altered Genomic DNA in Animals; Draft Guidance for Industry; Availability," *Federal Register* 82, no. 12 (January 19, 2017): 6561, https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-00839.pdf.

[27] Simultaneous calls with regards to updated guidance around genetically edited plants, and mosquitoes. "FDA Requests Comments on Documents Related to Certain Biotechnology and Mosquito-related Products," U.S. Food & Drug Administration, last modified June 20, 2017, https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm536949.htm.

[28] U.S. Department of Agriculture, Proposed Rule, "Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms," *Federal Register* 82, no. 214 (November 7, 2017): 51582, https://www.gpo.gov/fdsys/pkg/FR-2017-11-07/pdf/2017-24202.pdf.

[29] "Regulations.gov - Search Results," *Regulations.gov*, accessed December 14, 2017, https://www.regulations.gov/searchResults?rpp=25&po=0&s=FDA-2008-D-0394&dct=PS.

[30] National Academies of Sciences, Engineering and Medicine, *Preparing for Future Products of Biotechnology* (Washington DC: The National Academies Press, 2017), doi: 10.17226/24605.

[31] https://www.regulations.gov/document?D=FDA-2008-D-0394-0365

[32] Ibid.

[33] U.S. Department of Agriculture, Proposed Rule, "Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms," *Federal Register* 82, no. 12 (January 19, 2017): 7008, https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-00858.pdf.

[34] X.S. Liu, et al, "Editing DNA Methylation in the Mammalian Genome", *Cell*, 167 (2016): 233 - 247, https://www.nature.com/articles/537588c (accessed December 15 2017).

[35] U.S. Department of Agriculture, "Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms."