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Note

Genome-Edited Animals Are Not Transgenic Animals: Moving towards Responsible Research and Innovation with New Biotechnologies

*Yvie Yao**

INTRODUCTION

In November 2018, a Chinese scientist announced that he was the first person to use the gene-editing technique, CRISPR-Cas9, to create a genome-edited baby resistant to HIV, small pox, and malaria.[1] This alarming announcement immediately received criticism and concern from scientists around the globe.[2] Some of them questioned the technique of applying CRISPR-Cas9 to human embryos because of unknown gene-editing risks.[3] For example, knocking out the gene that controls HIV might render a person susceptible for West Nile Virus.[4] Some other scientists challenged the ethical implications of this move to produce "designer babies."[5] Marcy Darnovsky, executive director of the Center for Genetics and Society, lamented that "this

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1. *See* Rob Stein, *Chinese Scientist Says He's First to Create Genetically Modified Babies Using CRISPR*, NPR (Nov. 26, 2018, 5:02 AM), https://www.npr.org/sections/health-shots/2018/11/26/670752865/chinese-scientist-says-hes-first-to-genetically-edit-babies.

2. *See, e.g.*, Antonio Regalado, *Chinese Scientists Are Creating CRISPR Babies*, MIT TECH. REV. (Nov. 25, 2018), https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/ (noting that some scientists called the undertaking cause for "regret and concern over the fact that gene editing—a powerful and useful technique—was put to use in a setting where it was unnecessary.").

3. *See* Stein, *supra* note 11 (noting that applying CRISPR-Cas9 to embryos might introduce unknown, new diseases that could be passed down for generations).

4. *See id*.

5. *See id*.

amounts to unethical and reckless experimentation on human beings, and a grave abuse of human rights."[6]

CRISPR-Cas9 is a groundbreaking gene-editing technology that enables scientists to make precise changes in DNA more easily, quickly, and economically.[7] Scientists can now insert or delete certain genes at a specific site with the aid of CRISPR-Cas9.[8] As a result, this technology raises high hopes among scientists for major breakthroughs in all applications.[9] Meanwhile, the government and other experts assert that the current regulatory landscape in the United States over genome-edited products with new biotechnologies like CRISPR-Cas9—the Coordinated Framework for the Regulation of Biotechnology—may be inadequate to manage the risks associated with gene-editing techniques and their impacts on the environment and human health because existing regulations cannot keep up with the rapidly growing biotechnologies.[10]

Although the public does not yet need to be concerned with the application of CRISPR-like techniques on human embryos in the United States,[11] they will likely see CRISPR-edited food on

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6. Press Release, Ctr. for Genetics & Soc'y, Claim of Genetically Modified Babies: If True, a Grave Abuse of Human Rights (No v. 26, 2018), https://www.geneticsandsociety.org/press-statement/claim-genetically-modified-babies-if-true-grave-abuse-human-rights.

7. *See* Henry T. Greely, *Are We Ready for Genetically Modified Animals*, WORLD ECON. FORUM (Jan. 19, 2016), https://www.weforum.org/agenda/2016/01/are-we-ready-for-genetically-modified-animals/. Though this Note primarily focuses on CRISPR-Cas9, the discussion also applies to other CRISPR-like gene-editing technologies such as ZFNs and TALENs. *See* Daniel F. Voytas & Caixia Gao, *Precision Genome Engineering and Agriculture: Opportunities and Regulatory Challenges*, 12 PLOS BIOLOGY 1, 2 (2014).

8. *See* Tracey Tomlinson, *A CRISPR Future for Gene-Editing Regulation: A Proposal for an Updated Biotechnology Regulatory System in an Era of Human Genomic Editing*, 87 FORDHAM L. REV. 437, 445–46 (2018).

9. *See* Stein, *supra* note 1.

10. *See generally* MARCY E. GALLO ET AL., ADVANCED GENE EDITING: CRISPR-CAS9 (2018) (finding that "[r]egulatory gaps may lead to increased uncertainty that could slow down the development of future biotechnology products or result in a loss of public confidence in regulators.").

11. *See* Julia Belluz, *How Soon Will CRISPR Gene-edited Babies Come to the US?* VOX (Dec. 6, 2018), https://www.vox.com/science-and-health/2018/12/6/18126338/crispr-babies-china-gene-editing (noting that genetically-modified embryos are prohibited in the U.S. and offenders might face jail time and a $100,000 fine).

their plates in the very near future.[12] The first of these genome-edited crops—Cibus Canola—went on the market in 2018,[13] with more coming such as TALEN-edited soybeans that contain no trans fats.[14] Though genome-edited animals have not yet been approved for human consumption, a transgenic salmon—AquAdvantage Salmon—using the recombinant DNA technology has already been approved by the Food and Drug Administration (FDA).[15] Some scientists and environmental groups have raised ethical questions about the unintended ecological consequences of introducing a genetically modified organism into an open environment.[16]

Traditionally, the FDA has regulated genetically engineered animals for consumption under the new animal drug provisions of the Federal Food, Drug and Cosmetic Act (FD&C Act).[17] With its pronouncement of guidance #187 on intentionally altered genomic DNAs in 2017, the FDA also indicates that it inclines to regulate genome-edited animals with CRISPR-like technologies

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12. *See* Michael Le Page, *The Second Great Food War: Battle Lines Are Being Drawn Over Whether Crops and Animals Modified with CRISPR Gene Editing Can Make It onto Supermarket Shelves*, 239 NEW SCIENTIST 22 (2018) ("What we eat could be about to undergo a big change.").

13. *See* Frank Vinluan, *Cibus Raises $70M for Marketing of Gene-edited Canola, More R&D*, XCONOMY (June 27, 2018), https://xconomy.com/san-diego/2018/06/27/cibus-raises-70m-for-marketing-of-gene-edited-canola-more-rd/ (reporting that sales of Cibus' gene-edited canola went up).

14. *See* Caitlin Dewey, *The Future of Food: Scientists Have Found a Fast and Cheap Way to Edit Your Food's DNA*, WASH. POST (Aug. 11, 2018), https://www.washingtonpost.com/news/business/wp/2018/08/11/feature/the-future-of-food-scientists-have-found-a-fast-and-cheap-way-to-edit-your-edibles-dna/?utm_term=.be6680777901.

15. *See generally* U.S. FOOD & DRUG ADMIN., AN OVERVIEW OF ATLANTIC SALMON, ITS NATURAL HISTORY, AQUACULTURE, AND GENETIC ENGINEERING (updated Mar. 20, 2015), https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm222635.htm [https://wayback.archive-it.org/7993/20170404230805/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm222635.htm] [hereinafter USDA].

16. *See* Ocean Conservancy, et al., Citizen Petition Regarding AquaBounty Technologies' Application for Approval of Genetically Engineered Salmon (May 25, 2011), https://www.regulations.gov/document?D=FDA-2011-P-0448-0001.

17. In this Note, "genetically engineered animal" is a catchall phrase that refers to animals modified by rDNA techniques or other methods involving inserting DNA from one organism's genome into another organism's cell directly without any precise modification. *See* Guidance for Industry on Regulation of Genetically Engineered Animals Containing Heritable recombinant DNA Constructs, 74 FED. REG. 3057, 3057 (Jan. 16, 2009).

under the same provisions.[18] Yet, this guidance was not well received by various stakeholders.[19] Scientists and developers worry that the FDA's interpretation of altered genomic DNAs as animal drugs can stunt innovation of biotechnologies that will bring numerous benefits to the society.[20] In the meantime, nonprofits and other organizations disagree with the FDA's approach to treating genome-edited animals the same as transgenic animals, when in fact they pose different levels of risk.[21]

Therefore, the questions for this Note are whether the FDA's updated draft #187 provides legally sound mechanism for agency oversight of genome-edited animals and whether other regulatory pathways exist for agency oversight of genome-edited animals with new CRISPR-like biotechnologies under the current regulatory framework. Part I explains CRISPR-Cas9 and other precision gene-editing technologies, the history of the application of biotechnology on animals and the current development of genome-edited animals, U.S. regulatory framework on biotechnology, and the FDA's draft guidance #187. Part II discusses how the FDA's interpretation of altered genomic DNAs as animal drugs has exceeded its vested authority by Congress under existing statutes, how the FDA's approach deviates from the product-oriented regulatory approach, and how the FDA's issuance of the guidance document is inadequate to address biotechnology products that affect the environment and human health. Part III explores alternative

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18. *See* Regulation of Intentionally Altered Genomic DNA in Animals Draft Guidance, 82 FED. REG. 6561 (Jan. 19, 2017).

19. *Cf., e.g.*, Consumers Union, Comment Letter on the Food and Drug Administration's Draft Guidance for Industry #187 "Regulation of Intentionally Altered Genomic DNA in Animals" (June 19, 2017), https://www.regulations.gov/document?D=FDA-2008-D-0394-0431.

20. *See, e.g.*, Info. Tech. & Innovation Found., Comment Letter on the Food and Drug Administration's Draft Guidance for Industry #187 "Regulation of Intentionally Altered Genomic DNA in Animals" (Apr. 11, 2017), https://www.regulations.gov/document?D=FDA-2008-D-0394-0331.

21. *See, e.g.*, Ctr. for Food Safety, Comment Letter on The Food and Drug Administration's Draft Guidance for Industry #187 "Regulation of Intentionally Altered Genomic DNA in Animals" (June 19, 2017), https://www.regulations.gov/document?D=FDA-2008-D-0394-0427; *see also* Nat'l Ass'n of St. Dep't of Agric., Comment Letter on the Food and Drug Administration's Draft Guidance for Industry #187 "Regulation of Intentionally Altered Genomic DNA in Animals" (June 19, 2017), https://www.regulations.gov/document?D=FDA-2008-D-0394-0409.

pathways for agency oversight of genome-edited animals under the existing statutes and proposes that the White House updates the Coordinated Framework to incorporate the Responsible Research and Innovation (RRI) principle so as to address the risk of new biotechnological products while fostering public welfare-oriented responsible innovation with societal acceptability.

Notably, in focusing on the FDA's draft guidance to regulate intentionally altered genomic DNA, this Note is not intended to disrespect the FDA and its approach to protect the public health and food safety. Instead, this Note, using the FDA's guidance as an illustration, highlights the shortfalls of the current regulatory framework and its inability to adapt to the disruptive nature of technological development. In an environment of what some regulation scholars call "global innovation arbitrage,"[22] the answer to the "what is the right regulatory approach?" question is key to keep the U.S. competitive in biotechnological innovation while protecting citizens and human interest.

I. BACKGROUND

This Part of the Note provides background information on CRISPR-Cas9 as an illustration of precision gene-editing technologies, a brief survey of the development of animal biotechnologies, current regulatory structures for biotechnology in the United States, particularly the existing regulations over genetically engineered animals, and the FDA's attempt to cover genome-edited animals under the existing statutes through guidance #187. The background information of Part I will facilitate an understanding of the technical analysis of guidance #187 and shed light on reasons as to why the current regulatory framework cannot keep up with disruptive technologies like CRISPR-Cas9 which would be discussed later in detail.

A. WHAT IS CRISPR?

CRISPR, an acronym for Clustered Regularly Interspaced Short Palindromic Repeat, is an "organization of short, partially

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22. *See* Adam Thierer, *Global Innovation Arbitrage: Export Controls Edition*, THE TECH. LIBERATION FRONT (Jan. 2, 2019), https://techliberation.com/2019/01/02/global-innovation-arbitrage-export-controls-edition/ (defining global innovation arbitrage as the "idea that innovators can, and will with increasingly regularity, move to those jurisdictions that provide a legal and regulatory environment more hospitable to entrepreneurial activity.").

palindromic repeated DNA sequences" naturally found in bacteria.[23] First discovered in 1987, CRISPR was shown to be a successful bacterial defense mechanism against viruses twenty years later.[24] CRISPR is made up of two parts: repeats that are short sequences of DNA, and unidentical spacers that connect these repeats.[25] Also found within the bacterium are CRISPR-associated genes, known as Cas genes, which make Cas9 proteins that are able to unwind and cleave DNA.[26]

When a virus attacks a bacterial cell, some segments of the viral DNA will be copied and inserted as a new spacer into the existing bacterial CRISPR sequences.[27] Immediately, the CRISPR sequences that includes this new spacer from the viral DNA undergo a process of transcription—copying the double-chain helix structured DNA into a single-chain RNA.[28] The short segments of this long RNA transcribed from the original CRISPR sequences are CRISPR RNAs (crRNAs).[29] Should the same virus attack again, the Cas genes will be triggered to create Cas9 proteins. Then, the crRNAs will guide these Cas9 proteins to the invading virus because the crRNAs, with copies of the corresponding viral DNA, are able to match the viral genome.[30] These Cas9 proteins will then destroy the viral genome by unwinding its DNA and cutting up any DNA sequence that matches the crRNA sequence.[31]

In the field of genome editing, CRISPR refers to one of the many gene-editing technologies that enable scientists to make precise cuts along a cell's genome.[32] The CRISPR system consists

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23. *See* Ekaterina Pak, *CRISPR: A Game-Changing Genetic Engineering Technique*, HARV. U. GRADUATE SCH. OF ARTS & SCI. (July 31, 2014), http://sitn.hms.harvard.edu/flash/2014/crispr-a-game-changing-genetic-engineering-technique/.

24. 24. *See generally* GALLO ET AL., *supra* note 10, at 32 (2017) (providing a chronology of discoveries and milestones in the development of CRISPR-Cas9).

25. *See* Bozeman Science, *What Is CRISPR?*, YOUTUBE (Feb. 18, 2016), https://www.youtube.com/watch?v=MnYppmstxIs.

26. *See id.* Cas proteins convert chemical energy into mechanical forces in response to specific stimuli. Pak, *supra* note 23.

27. *See* Pak, *supra* note 23.

28. *See id.*

29. *See id.*

30. *See* Bozeman Science, *supra* note 25.

31. *See id.*

32. *See* Tomlinson, *supra* note 8, at 443 ("CRISPR is used as a catchall term for systems that enable researchers to program the CRISPR molecule to make

of two components: the Cas9 protein and a guide RNA that can recognize the sequence of DNA to be edited.[33] Scientists are able to create guide RNAs that match specific DNA sequences to be edited in a cell, just like how CRISPR in a bacterium generates crRNAs.[34] Scientists then attach these artificially created guide RNAs to the DNA-cutting protein Cas9 and introduce this complex into the target cell.[35] The guide RNAs will direct the enzyme Cas9 to the targeting DNA sequence at a specific site, allowing it to unwind the double helixes and subsequently matching to the single-stranded DNA sequence.[36] When the match completes, Cas9 will cut the targeted DNA sequence; once the host DNA is broken, the gene will be successfully inactivated or deleted.[37] Scientists can also add a new RNA sequence to where the host DNA is cut; by doing this, they successfully add genetic material to the target cell.[38] After these intentional edits, scientists rely on a cell's own ability to repair its DNA sequence.[39] With the CRISPR-Cas9 system, scientists can finally edit the existing genome by deleting or inserting DNA sequences at a precise location.[40]

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precise cuts along a cell's genome."). *See* Voytas & Gao, *supra* note 7, at 2 (introducing other types of genome-editing technologies that are similar to CRISPR which include engineered homing endonucleases or meganucleases, zinc finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs)).

33. *See* GALLO ET AL., *supra* note 10, at 2–3 (explaining how the CRISPR-Cas9 system functions).

34. *See id.*

35. *See id.*

36. *See id.*

37. *See* Evita V. Grant, *FDA Regulation of Clinical Applications of CRISPR-CAS Gene-Editing Technology*, 71 FOOD & DRUG L.J. 608, 611 (2016) (explaining that the CRISPR-Cas system can "recognize and cleave a specific sequence of DNA, allow[ing] it to be developed into artificial restriction enzymes that can be used to alter specific sites of DNA in any organism.").

38. *See id.*

39. *See* U.C. BERKELEY, *DNA Repair After CRISPR Cutting Not at All What People Think*, PHYS.ORG (Jul. 30, 2018), https://phys.org/news/2018-07-dna-crispr-people-thought.html (explaining two types of repair: non-homologous end-joining repair and homology-directed repair).

40. *See* Tomlinson, *supra* note 8, at 445–46 (claiming that CRISPR is the "most advanced gene-editing technology currently available" that enables "scientists to edit the human genome in previously impossible ways.").

B. CRISPR-LIKE TECHNOLOGIES ARE DIFFERENT FROM TRANSGENESIS TECHNIQUES

This newly evolved CRISPR-Cas9 system, along with other gene-editing technologies,[41] differs from transgenesis which directly inserts a copy of genetic material with a specific trait from a donor organism into a cell of a recipient organism.[42] Transgenesis, however, does not control the site in the genome where the inserted material will end up and can result in random consequences.[43] Unlike traditional genetic engineering with transgenic techniques, scientists can precisely edit a single sequence of the genome at a very specific site with CRISPR-Cas9.[44] Thus, CRISPR-Cas9 is at least 10 times more accurate and predictable.[45] It can also democratize biotechnology because anyone with basic knowledge and skills in molecular biology can, theoretically, perform a CRISPR cutting.[46]

Furthermore, CRISPR-Cas9 is often viewed less as an artificial process but a mechanism "mimicking a natural mutation."[47] This is because gene-editing does not require the transfer of DNA from one organism to another but capitalizes on a cell's natural defense mechanism to induce "a specific change

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41. *See* Voytas & Gao, *supra* note 32 and accompanying text.

42. *See* Leslie Pray, *Recombinant DNA Technology and Transgenic Animals*, 1 NATURE EDUC. 51 (2008) (discussing inserting foreign DNA into a new host cell).

43. *See* GMO Answers, *How Are GMOs Created? | The Hawaiian Rainbow Papaya Story*, YOUTUBE (Aug. 2, 2013), https://www.youtube.com/watch?v=2G-yUuiqIZ0&t=234s.

44. *See* Ken Kingery, *What Is CRISPR, and How Has It Changed Genetic Research?*, WORLD ECON. FORUM (Oct. 30, 2015), https://www.weforum.org/agenda/2015/10/what-is-crispr-and-how-has-it-changed-genetic-research/ ("The primary advantage of CRISPR over previous technologies is the ability to use a genetic scalpel rather than a sledgehammer[.]"); *see also* Greg Licholai, *Is CRISPR Worth the Risk?*, YALE INSIGHTS (Aug. 21, 2018), https://insights.som.yale.edu/insights/is-crispr-worth-the-risk ("What was previously attempted with gene editing was . . . kind of like trying to edit a book by only being able to rip out a page at a time and transfer a page at a time . . . . [T]his technology . . . literally comes down to the individual letters.").

45. *See* Greely, *supra* note 7 ("DNA editing had been done in laboratories for about 40 years, but CRISPR/Cas9 is at least 10 times more accurate, faster, easier and less expensive.").

46. *See* Grant, *supra* note 37, at 626–27 (describing CRISPR as accessible, easy to use and affordable).

47. Ann Bruce, *Genome Edited Animals: Learning from GM Crops?*, 26 TRANSGENIC RES. 385, 389 (2017).

at a precise location in the genome."[48] Despite their accuracy and accessibility, CRISPR-like technologies could potentially result in off-target effects when the Cas9 enzyme snips at similar non-target sites.[49] Scientists have developed various strategies to contain such effects.[50] This Note, however, will not go into details discussing various shortfalls of CRISPR-like technologies and how scientists have adopted measures to tackle these problems.[51]

C. HISTORICAL OVERVIEW OF GENETICALLY ENGINEERED ANIMALS BEFORE CRISPR-LIKE TECHNOLOGIES

Looking back at the development of biotechnology, it is not hard to find the application of biotechnology on animals; in fact, animal biotechnology has been around for centuries.[52] Before the late nineteenth century, human-directed breeding was the dominant method for the selection of animals that match particular production traits and purposes suited to a specific climate.[53] In the next fifty years, the farm animal industry witnessed a growing array of reproductive biotechnologies, such

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48. *See id.* at 391 (arguing that "genome editing does not transgress species barriers" but does "require a deliberate intervention that is outside natural mutation.").

49. *See generally* Ellen Shrock & Marc Güell, *CRISPR in Animals and Animal Models*, *in* 152 PROGRESS IN MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE 1, 97 (Raúl Torres-Ruiz & Sandra Rodriguez-Perales eds., 2017) (discussing that off-target effects might cause chromosomal deletions, inversions, or translocations).

50. *See* Wenfang Tan, et al., *Gene Targeting, Genome Editing: From Dolly to Editors*, 25 TRANSGENIC RES. 273, 283 (2016) (providing examples to control off-site effects such as masking Cas9 with a fusion peptide, preventing activity until cleaved by a small molecule, expanding the TALEN RDV repertoire, dimerizing the editing enzyme, etc.).

51. Excellent articles in the last few years have detailed the shortfalls of CRISPR-Cas9. *See* Michael Kosicki, Kärt Tomberg & Allan Bradley, *Repair of Double-Strand Breaks Induced by CRISPR-Cas9 Leads to Large Deletions and Complex Rearrangements*, 36 NATURE BIOTECHNOLOGY 765 (2018); *see also* Heidi Ledford, *CRISPR Gene Editing Produces Unwanted DNA Deletions*, NATURE (Jul. 16, 2018), https://www.nature.com/articles/d41586-018-05736-3.

52. *See* Heiner Niemann & Bob Seamark, *The Evolution of Farm Animal Biotechnology*, *in* ANIMAL BIOTECHNOLOGY 1: REPRODUCTIVE BIOTECHNOLOGIES 1, 1–8 (Heiner Niemann & Christine Wrenzycki eds., 2018) (discussing "Domestication", "Systematic Breeding", and "Scientifically-based Breeding" as forms of animal biotechnology).

53. *See id.* at 3 ("[H]uman-directed breeding results in the abundance of great phenotypic and genetic variation in domesticated animals including, for example, the more than 3,000 cattle and 1,300 pig breeds").

as artificial insemination.[54] Artificial insemination has replaced traditional breeding methods for breeders and "remain[ed] the primary method . . . around the globe [] to improve the genetic quality of their animals . . . ."[55]

In the next twenty years, researchers have applied this DNA analysis to animal breeding, using quantitative trait loci (QTL) to identify causal mutations for specific traits.[56] Soon, a new era in animal breeding began with the creation of the first transgenic pigs and sheep.[57] Transgenesis can be achieved by microinjection of a foreign DNA into an oocyte—an immature egg cell of the animal ovary—shortly after fertilization.[58] Transgenesis, nevertheless, faced a few limitations, the primary one being that the introduced DNA could only be integrated randomly in the recipient genome.[59] As of today, there is already

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54. *See id.* at 5 (showcasing that under these emerging reproductive biotechnologies, genetics has been applied to animal breeding, which has helped identify inheritable chemical or molecular markers that could be used to guide breeding technologies and promote genetic change in economically important productive traits).

55. *See id.* at 10 ("[Artificial Insemination] is employed in more than 90% of all sexually mature female dairy cattle in countries with well-advanced breeding programs . . . . [t]he adoption of [artificial insemination] for use with low unit cost animals such as sheep and goats is less widespread but is still employed in the breeding of greater than 3.3 million sheep and 0.5 million goats annually").

56. *See id.* at 7–8 (finding that the QTL strategy was succeeded by marker-assisted selection which includes the detection of several QTLs, followed by identification of the gene which causes the respective mutation and finally the increase of the frequency of the favorable allele by selection).

57. *See* Niemann & Seamark, *supra* note 52, at 19 ("[I]ntroducing new and functional genetic material into the germline of laboratory rodents heralded a new era in animal breeding."). *See generally* Götz Laible, *Production of Transgenic Livestock: Overview of Transgenic Technologies*, *in* ANIMAL TECHNOLOGY 2: EMERGING BREEDING TECHNOLOGIES 95, 95–113 (Heiner Niemann & Christine Wrenzycki eds., 2018) (discussing transgenic livestock).

58. *See* Laible, *supra* note 57, 95–113 (introducing two types of transgenic technologies: the embryo-mediated approach refers to the introduction of the genetic modification into an embryo whereas the cell-mediated approach refers to the introduction of genetic information into a cell which "is subsequently used to generate an entire animal based on the genetics of this cell.").

59. Niemann & Seamark, *supra* note 52, at 19. *See* Laible, *supra* note 57, at 101–02 (finding that "only 70% of transgenic founder animals were able to transmit the transgene through the germline to the next generation" and that the process is inefficient and very expensive).

one transgenic animal approved for human consumption in the United States—AquAdvantage Salmon.[60]

D. EMERGING APPLICATIONS OF CRISPR-LIKE TECHNOLOGIES ON ANIMALS

The CRISPR-Cas9 system has overcome the many limitations transgenesis faced and has been used to create a wide variety of genome-edited animals, such as pigs, cattle, goats, and sheep.[61] Unlike transgenesis which might lead to random consequences from the combination of the donor organism's DNA with the recipient organism's cell, CRISPR-Cas9 is able to edit an animal's genome in a precise manner to obtain a targeted trait.[62] Consequently, genome-edited animals created from CRISPR-like technologies play an important role in "highly diverse areas such as food improvement, disease resistance, and human disease models."[63] For instance, AgGenetics has engineered Angus cows to produce a certain type of hair that will allow them to adapt to warmer climates and thus increase Angus beef's yields.[64] Recombinetics has also gene-edited a hornless breed of cattle, freeing it from using hot irons to burn off horns during food processing and significantly improving animal welfare.[65] Moreover, CRISPR-Cas9 has also

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60. *See* Heidi Ledford, *Transgenic Salmon Leaps to the Dinner Table*, 527 NATURE 417 (2015). *See generally,* USDA, *supra* note 15 (illustrating that AquAdvantage fish produce extra growth hormone which allows them to grow to market size in eighteen months rather than the usual three years).

61. *See generally* Shrock & Güell, *supra* note 49, at 98–105 (outlining three methods of using the CRISPR-Cas9 system on animals); Tan, *supra* note 50, at 277 (listing all genome-edited animals in a table); s*ee* Gavin J. Knott & Jennifer A. Doudna, *CRISPR-Cas Guides the Future of Genetic Engineering*, 361 SCI. 866, 867 (2018) (discussing applications of CRISPR to biomedical and clinical research, such as engineering T cells as a prelude to developing advanced immunotherapies to target cancers and targeting the genetic basis for sickle cell disease); *see* GALLO, *supra* note 24, at 20 (explaining that CRISPR has also been widely applied to agricultural development, such as better plant-pest control, new and enhanced nutritional characteristics, and plant varieties that could be grown on marginal lands or in poor quality soils).

62. *See supra* Section I.B.

63. Bjoern Petersen, *DNA Nucleases and their Use in Livestock Production*, *in* ANIMAL BIOTECHNOLOGY 2: REPRODUCTIVE BIOTECHNOLOGIES 123, 124 (Heiner Niemann & Christine Wrenzycki eds., 2018).

64. *See* Shrock & Güell, *supra* note 49, at 104.

65. *See id.* (providing additional examples such as genetically modified chickens which produce non-allergen eggs, pigs resistant to the Porcine Reproductive and Respiratory Syndrome Virus, and cattle are resistant to

been used to produce genome-edited pets that contain custom traits.[66] Overall, CRISPR-Cas9 has significantly accelerated the creation of animals with novel traits that may be beneficial for agricultural production and animal health.[67]

E. CURRENT REGULATORY FRAMEWORK FOR BIOTECHNOLOGY IN THE U.S.

The federal government has a long history of regulating biotechnology. It first came up with a set of research guidelines in the 1970s in response to the emerging recombinant DNA research for transgenesis technologies.[68] In the next eight years, Congress made many attempts to enact a unified biotechnology legislation to address the emerging genetic manipulation techniques.[69] In 1984, the White House Cabinet Council on

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bovine tuberculosis). *See generally* Adam Shriver & Emilie McConnachie, *Genetically Modifying Livestock for Improved Welfare: A Path Forward*, 31 J. AGRIC. ENV'T ETHICS 161 (2018) (arguing that modern biotechnologies improve animal welfare).

66. *See* Shrock & Güell, *supra* note 49, at 105 (providing examples of very small pigs as pets and dogs with improved running ability).

67. *See, e.g., id.* at 101 ("The uses of CRISPR–Cas9 for animal genome engineering include . . . the inactivation or alteration of genes in model animals in order to elucidate the functions of these genes . . . the production of animal models of human disease to study disease progression in a controlled manner and evaluate potential therapies . . . and the use of genetically modified animals for industrial, pharmaceutical, and biotechnological production"); Bruce, *supra* note 47, at 387–88; Zahra Meghani & Jennifer Kuzma, *Regulating Animals with Gene Drive Systems: Lessons from the Regulatory Assessment of a Genetically Engineered Mosquito*, 5 J. RESPONSIBLE INNOVATION 203 (2018) (discussing gene drives); George Washington University Regulatory Studies Center, Comment Letter on The Food and Drug Administration's Draft Guidance for Industry #187 "Regulation of Intentionally Altered Genomic DNA in Animals" (June 19, 2017), https://www.regulations.gov/document?D=FDA-2008-D-0394-0416 (listing CRISPR projects that involve resurrecting lost species, protecting extremely endangered species, increasing agricultural productivity and controlling human disease dependent on wild animal hosts); Veronique Greenwood, *How CRISPR Is Spreading Through the Animal Kingdom*, PBS.ORG (May 23, 2018), https://www.pbs.org/wgbh/nova/article/crispr-animals/.

68. *See* NAT'L ACAD. OF SCI., ENG'G, AND MED., PREPARING FOR FUTURE PRODUCTS OF BIOTECHNOLOGY 69 (2017) (explaining that the National Institutes of Health published a set of research guidelines in 1976 as the prototype of the federal regulatory framework, applied to all research with recombinant or synthetic nucleic acid molecules).

69. *See* WHITE HOUSE, MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS: FINAL VERSION OF THE 2017 UPDATE TO THE COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY 3 (2017) (explaining that enhanced characteristics of food, manufactured food, waste

Natural Resources and the Environment formed a working group on biotechnology which proposed a coordinated framework to address products developed from new technologies.[70]

In 1986, the White House issued the nation's first regulatory document about genetically engineered products, *Coordinated Framework on the Regulation of Biotechnology* (Coordinated Framework), which clarified the regulatory authority and responsibility of each federal agency regarding products derived from new biotechnologies.[71] The framework identified a lead agency among the agencies responsible for regulation of a specific product category or use: the FDA regulates the safety of all food and cosmetic products sold for human use; the Department of Agriculture (USDA) regulates the production and marketing of products grown on farms; and the Environment Protection Agency (EPA) regulates actual and potential threats to human health resulting from disruption of the environment.[72]

The Coordinated Framework also established three essential tenets: (1) U.S. regulatory policy over biotechnological products would be product-based instead of process-based;[73] (2) only regulation grounded in verifiable scientific risks would be tolerated;[74] (3) existing statutes are sufficient to review new products, meaning that statutes enacted before this framework

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disposal, medicine and pesticides rely upon new techniques such as recombinant DNA, recombinant RNA, and cell fusion).

70. *See id.* at 70 (orchestrating the biotechnology-related responsibilities of multiple federal agencies).

71. Executive Office of the President, *Coordinated Framework for Regulation of Biotechnology*, 51 FED. REG. 23302, at 23303 (June 26, 1986).

72. WHITE HOUSE, *supra* note 69, at 28 n.77; Edward L. Rubin & Joanna K. Sax, *Administrative Guidance and Genetically Modified Food*, 60 ARIZ. L. REV. 539, 554 (2018).

73. *See* Zahra Meghani, *Genetically Engineered Animals, Drugs, and Neoliberalism: The Need for a New Biotechnology Regulatory Policy Framework*, 30 J. AGRIC. ENV'T ETHICS 715, 733 (2017) ("Regulation by the FDA must be based on the rational and scientific evaluation of products, and not on a priori assumptions about certain processes."); Rubin & Sax, *supra* note 72, at 555 (focusing on the characteristics and risk posed by the introduction, rather than on the process by which a product is created).

74. Eric E. Williams, *CRISPR: Redefining GMOs—One Edit at a Time*, 39 U. ARK. LITTLE ROCK L. REV. 437, 451 (2017). *See generally* NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 69 ("Regulatory risk assessment . . . [identifies] possible causes of harm . . . the relationship between exposure to the harm and the probability of the adverse effect . . . the extent of human or environmental exposure to the harm, and . . . the probability of the harm occurring and the magnitude of the possible harm[.]").

were interpreted to cover biotechnology.[75] Under this framework, the federal government sought to "achieve a balance between regulation adequate to ensure the protection of health and the environment while maintaining sufficient regulatory flexibility to avoid impeding innovation."[76] In 1992, the Coordinated Framework was updated to reaffirm a scientific, risk-based, and product-based approach consistent with the 1986 Coordinated Framework.[77]

Almost twenty years later, the White House updated the Coordinated Framework in 2017 in response to the accelerating development and application of precise gene-editing biotechnologies.[78] In the past decade, there were growing concerns regarding whether products developed using new technologies such as CRISPR-Cas9 would fall outside the scope of existing regulations and what factors should be considered to assess risks.[79] Thus, the 2017 update attempted to clarify: (1) what biotechnology product areas are regulated; (2) what roles each agency plays for different product areas; (3) how agencies communicate and coordinate with each other; and (4) what reviewing and updating mechanism each agency should adopt.[80] This update reaffirmed the tenets established under the 1986 Coordinated Framework that regulations should be product-

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75. *See* Meghani, *supra* note 73, at 733 (arguing that the working group chose existing statutes because of the considerations of "immediate regulatory protection and certainty" for the biotechnology companies which the state believed to be in the interest of the U.S. on the global arena).

76. WHITE HOUSE, *supra* note 69, at 4.

77. Meghani, *supra* note 73, at 735–37. *See* NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 70 (evaluating the risk-based assessment based on the characteristics of the organism, the target environment, and the type of application).

78. WHITE HOUSE, *supra* note 69. *See* NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 70 (providing a basic survey of statutory authorities of the EPA, the FDA, and the USDA to regulate environmental and human health and safety risks related to biotechnology products).

79. *See* Emily Waltz, *A Face-lift for Biotech Rules Begin*, 33 NATURE BIOTECH., 1221 (2015) (explaining contexts for the 2017 update); Kelly Servick, *U.S. to Review Agricultural Biotech Regulations*, 349 SCI. 131 (2015) (finding the outdated framework has resulted in puzzling regulatory paths and a new framework would help clarify each agency's role and strategy); s*ee* Heidi Ledford, *Gene-editing Surges as US Rethinks Regulations*, NATURE (Apr. 12, 2016), https://www.nature.com/news/gene-editing-surges-as-us-rethinks-regulations-1.19724 (considering that gene-edited products would fall outside the scope of existing regulation).

80. WHITE HOUSE, *supra* note 69, at 1–2.

based,[81] the regulatory system should be grounded in risk assessment,[82] and existing statutory authorities of each agency are sufficient to cover biotechnology products and their applications.[83] Importantly, the update ceased to identify lead agencies which had caused confusion and been mistakenly interpreted; instead it encouraged coordination and communication among agencies and clarified "current responsibilities and the relevant coordination across [the] EPA, [the] FDA, and [the] USDA for the regulatory oversight of [different] biotechnology products."[84] With such an upgrade in the federal biotechnology regulatory system, the federal government believed that it would "increase public confidence in the regulatory system and prevent unnecessary barriers to future innovation and competitiveness."[85]

Despite the federal government's attempt to clarify the roles of each agency, the 2017 update still left each agency with significant flexibility to determine whether it has regulatory authority over certain genome-edited products under existing statutes. Guided by the updated Coordinated Framework, the agencies have made respective changes to their regulation of genome-edited products.[86] For example, the FDA has read the existing statutes to cover genome-edited animals whereas the USDA has proactively excluded certain genome-edited organisms that are modified solely by genetic deletions from its regulatory review.[87] Even though the Coordinated Framework confers considerable flexibility to the agencies, existing statutes

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81. *Id.* at 8 ("Exercise of agency oversight within the scope afforded by statutes should be commensurate with the risk posed by the introduction of the biotechnology product and should not turn on the fact that it was created or has been altered by a particular process or technique.").

82. *Id.* at 7 ("It is the characteristics of the biotechnology product, the environment into which it will be introduced, and the application of the product that determine its risk (or lack thereof).").

83. *Id.* ("Each agency uses its existing statutory authorities and regulations to ensure the safety of the biotechnology products for their intended applications. Underlying statutes define the boundaries of the scope of oversight afforded to each regulatory agency.").

84. *Id*. at 28.

85. WHITE HOUSE, *supra* note 69, at 1.

86. Emily Marden & Deepti A. Kulkami, *Regulatory Pathways Emerged for Gene-edited Products*, LAW360 (Mar. 20, 2017), https://www.law360.com/articles/903715/regulatory-pathways-emerge-for-gene-edited-products.

87. *Id.*

might not equip regulators with the best tools to regulate emerging biotechnological products effectively since gene-editing technologies were not contemplated by Congress when these statutes were passed and amended.[88]

F. CURRENT REGULATORY PATHWAYS OF GENETICALLY ENGINEERED ANIMALS WITH NON-CRISPR-LIKE TECHNOLOGIES

Within the Coordinated Framework, genetically engineered animals using recombinant DNA or other similar technologies are regulated under different agencies with different statutory authorities according to their product area applications. Below is an outline of various existing regulatory pathways of genetically engineered animals.[89]

i. New Animal Drugs

In 2009, the FDA published a guidance regulating genetically engineered animals under the new animal drugs provisions under the FD & C Act by treating genetic material that is integrated into the animal as a new animal drug.[90] The FDA followed the risk-based assessment laid out under the Coordinated Framework, considering the introduced DNA's impact on animal health, effectiveness to the animal and, in the case of food-producing animals, whether food derived from the animal is safe for consumption.[91] Under this guidance, the FDA

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88. *See* NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 173 (acknowledging that "in some cases the jurisdiction of the agencies has the potential to leave gaps in regulatory oversight.").

89. This Note also recognizes that the FDA regulates therapeutic and xenotransplantation products for human use derived from transgenic animals through guidance. Genetically engineered animals are also covered by applicable federal, state, local, and tribal laws pertaining to humane care, environmental safety, import and export, etc. This Note, however, does not go into detailed discussions of these regulations.

90. *See* 21 U.S.C. § 321(g)(1) (2018) ("The term 'drug' means: . . . (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals."). 21 U.S.C. § 321(v) (2018) ("The term 'new animal drug' means any drug intended for use for animals other than man . . . ."); Guidance for Industry on Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs, *supra* note 17 (maintaining that the rDNA construct in a genetically engineered animal that is intended to affect the structure or function of the body of the animal meets the FD & C Act's drug definition).

91. *See* Guidance for Industry on Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs, *supra* note 17. WHITE HOUSE, *supra* note 69, at 19 (listing the seven categories that the FDA

has approved three animals,[92] including the genetically engineered salmon for human consumption.[93]

ii. New Drugs

Under the FD & C Act, the FDA also has regulatory authority over new drugs that are developed through genetic engineering,[94] which include drugs produced from genetically engineered animals.[95] The FDA has developed regulations to evaluate whether the drug is safe and effective and whether the benefits outweigh the risks of the drug.[96]

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applied in its review process: product definition, molecular characterization of the construct, molecular characterization of the GE animal lineage, phenotypic characterization of the GE animal, durability plan, environmental and food/feed safety, and claim validation); the FDA should also conduct an environmental assessment under the National Environmental Policy Act "with its approval of genetically engineered animals under its animal drug licensing authority and seek measures to ameliorate any anticipated adverse environmental effects." NAT'L ACADS., ANIMAL BIOTECHNOLOGY: SCIENCE-BASED CONCERNS 164 (2002).

92. *See* Sarah Polcz & Anna C.F. Lewis, *A Menagerie of Moral Hazards: Regulating Genetically Modified Animals*, 46 J. L. MED. & ETHICS 180, 183 (2018) (including a goat that produces an anticlotting protein in its milk, a chicken whose eggs contain a drug for a specific cholesterol disease, and salmon that grows faster than normal).

93. *See* Ledford, *supra* note 60. *Compare AquAdvantage Salmon Approval Letter and Appendix*, U.S. FOOD & DRUG ADMIN. (updated Dec. 1, 2017), https://www.fda.gov/AnimalVeterinary/ucm466214.htm, *and Freedom of Information Summary*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/downloads/animalveterinary/developmentapprovalprocess/geneticengineering/geneticallyengineeredanimals/ucm466215.pdf, *with* S. 230, 112th Cong. (1st Sess. 2011) (proposing to amend the FD & C Act to prevent approval of the genetically engineered salmon), *and* H.R. 521, 112th Cong. (1st Sess. 2011) (preventing approval of the genetically engineered salmon).

94. *See* 21 U.S.C. § 321(p) (2018) (defining the term new drug as "any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized . . . as safe and effective for use . . . .").

95. *See, e.g.*, Justin Caba, *FDA Finally Approves the First Drug to Treat Rare Genetic Disease, Hereditary Angioedema*, MED. DAILY (July 17, 2014), https://www.medicaldaily.com/fda-finally-approves-first-drug-treat-rare-genetic-disease-hereditary-angioedema-293656 (reporting that the FDA approved a drug collected from the milk of lab-made rabbits to treat a genetic disease that causes body swelling).

96. *See generally* 21 U.S.C. § 355 (2018).

iii. Biologics

Under the Public Health Service Act, the FDA regulates biological products that are produced from genetically engineered animals.[97] These biologics must be licensed by the FDA which considers whether they are safe and effective for their intended purpose.[98]

iv. Animal Pests

With the authority from the Animal Health Protection Act, the USDA has developed a framework to regulate genetically engineered animals by prohibiting or restricting imports or entry and interstate movement of them if they are animals that are considered livestock and that serve as animal pests transmitting diseases.[99] The regulatory framework does not distinguish genetically engineered animals from non-genetically engineered animals; the USDA, when deciding whether to issue a permit for importing or transporting animal pests, considers the animal health risk and the mitigations that can be applied to reduce this risk.[100]

v. Others

The FDA and the USDA also share regulatory responsibility to ensure food from genetically engineered animals for human consumption is safe, wholesome, and correctly labeled.[101]

Besides the FDA's attempt to cover genetically engineered animals under the FD & C Act by categorizing inserted foreign

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97. *See* 42 U.S.C. § 262(i)(1) (2017) ("The term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.").

98. *See generally* 42 U.S.C. §§ 262–263a-7 (1992).

99. *See* 7 U.S.C. § 8302(13) (2018) ("The term 'pest' means any of the following that can directly or indirectly injure, cause damage to, or cause disease in livestock: . . . (J) A vector. (K) Any organism similar to or allied with any of the organisms described in this paragraph."); Framework for the Regulation of Genetically Engineered Animals and Insects Pursuant to the Animal Health Protection Act, https://www.aphis.usda.gov/animal_health/downloads/framework-ee-ahpa.pdf.

100. *See* Framework for the Regulation of Genetically Engineered Animals and Insects Pursuant to the Animal Health Protection Act, *supra* note 99.

101. *See* NAT'L ACADS., *supra* note 91, at 163 (including the FD & C Act, the Federal Meat Inspection Act, and the Poultry Products Inspection Act).

DNA sequences as a new animal drug,[102] all the other regulations by various agencies have not stirred up controversies because they regulate genetically engineered animals in a way that are not distinguishable from non-genetically engineered animals.

G. THE FDA'S UPDATED GUIDANCE OVER GENOME-EDITED ANIMALS WITH CRISPR-LIKE TECHNOLOGIES

In January 2017, as part of the federal efforts to update the Coordinated Framework where the government was concerned that new biotechnological products would slip off the existing regulatory framework,[103] the FDA published a draft updated guidance #187 which interprets the new animal drug provisions under the FD & C Act to cover products developed from CRISPR-like precision gene-editing technologies.[104] As explained in section F above, the previous guidance only addressed transgenic animals, but not genome-edited animals created with CRISPR-like technologies that result in "targeted DNA sequence changes including nucleotide insertions, substitutions, or deletions," because the regulatory framework had not adapted to the development of new technologies.[105] Thus, this new draft guidance is the FDA's attempt to clarify that the altered genomic DNA in an animal is "an article that meets the definition of a new animal drug at each site in the genome where the alteration (insertion, substitution or deletion) occurs" and therefore shall

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102. *See, e.g.*, GTC Biotherapeutics, Inc., Comment Letter on Food and Drug Administration Notice (Nov. 15, 2018), https://www.regulations.gov/document?D=FDA-2008-D-0394-0173 (arguing that "the [] Guidance stretches a proper interpretation of the law"); John J. Cohrssen & Henry I. Miller, *Current FDA Approach to Genetically Engineered Animals Is Flawed*, THE HILL (Nov. 6, 2017), https://thehill.com/opinion/healthcare/358893-current-fda-approach-to-genetically-engineered-animals-is-flawed (categorizing the rDNA technology as one of the many animal breeding techniques and arguing that the animal drug provisions impose high evidentiary standard on developers).

103. *See* Waltz, *supra* note 79 and accompanying texts.

104. *See* Regulation of Intentionally Altered Genomic DNA in Animals Draft Guidance, *supra* note 18. *See* Nick Stockton, *The FDA Wants to Regulate Edited Animal Genes as Drugs*, WIRED (Jan. 24, 2017), https://www.wired.com/2017/01/fda-wants-regulate-edited-animal-genes-drugs/.

105. Regulation of Intentionally Altered Genomic DNA in Animals Draft Guidance, *supra* note 18.

be covered by the FDA's regulatory authority.[106] Yet, this guidance has faced an unanticipated outcry from researchers, biotechnological companies, various environmental and industry groups, as well as other federal agencies.[107] Part II will discuss the pitfalls of this guidance and propose alternative regulatory pathways for genome-edited animals if the FDA does not have the regulatory authority to do so.

II. ANALYSIS

Notably, current regulatory structures are not set up to regulate CRISPR-like technologies.[108] This Part recognizes the FDA's efforts to close the gaps under the current Coordinated Framework to regulate genome-edited animals with CRISPR-like technologies through guidance #187 but argues that the FDA has exceeded its vested statutory authority under the FD & C Act which was passed in 1938. Furthermore, the FDA's approach signals a departure from the product-based and risk-based approach set in the Coordinated Framework. Rather, the FDA focuses on the process from which genome-edited animals are created. Moreover, instead of notice-and-comment rulemaking, the FDA has chosen to issue a guidance document that might not be adequate to address biotechnology products and the impacts of their application on the environment and human safety. Importantly, it is crucial to recognize that regulating more than necessary and implementing a stringent regulatory system will stifle innovation and shun scientists away while leaving a genome-edited product completely outside of regulatory oversight will be equally worrisome and stir up public concerns. Therefore, a balance must be struck between the competing concerns.

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106. *Id. Cf.* George Washington University Regulatory Studies Center, *supra* note 67 (noting that the guidance, however, excludes random mutagenesis followed by phenotypic selection).

107. *See, e.g.*, Williams, *supra* note 74, at 454 (contending that researchers were hopeful that these gene-editing products would be regulated less stringently than animals that are genetically engineered by introducing foreign DNA).

108. *See* Greely, *supra* note 45 (noting that current statutes do not cover all that CRISPR can accomplish); Brooke Borel, *The U.S. Regulations for Biotechnology Are Woefully Out of Date*, SLATE (Apr. 21, 2017), http://www.slate.com/articles/technology/future_tense/2017/04/u_s_biotechnology_regulations_are_woefully_out_of_date.html.

A. THE FDA EXCEEDED ITS VESTED STATUTORY AUTHORITY TO INTERPRET ALTERED GENOMIC DNAS AS NEW ANIMAL DRUGS.

Congress expressly delegated the authority of regulating new animal drugs to the FDA under the FD & C Act which sets the boundaries of the FDA's scope of regulation.[109] The FDA has exceeded its vested authority by interpreting altered genomic DNAs as new animal drugs.[110] Under the FD & C Act, a new animal drug is defined as "any drug intended for use for animals other than man . . . . ."[111] To qualify as a new animal drug, the application must be a drug first which means an "article[] intended to affect the structure or any function of the body of man or other animals."[112] The FDA characterizes genome-edited animals as equivalent to transgenic animals and thus treats altered genomic DNA as the regulated article.[113] However, many industry groups or nonprofits disagree with the FDA's characterization and argue that the FDA's attempt to assert jurisdiction over the production and commercialization of genome-edited animals is *ultra vires* because altered genomic DNAs could not or would not be drugs.[114]

When the FDA issued the 2009 guidance to exercise oversight of the recombinant DNA construct to an animal as new animal drugs based on which it approved several transgenic animals, it was already testing the limit of the scope of authority vested by Congress under the FD&C Act. In the FDA's most recent guidance, however, it has moved past the tipping point because under certain circumstances CRISPR-like technologies do not involve insertion of foreign DNAs into the genome of a targeted animal.

The FDA's interpretation of a drug is erroneous. Under the FD&C Act, a drug must be an article "intended to affect the structure or any function of the body of man or other animals."[115]

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109. *See generally* 21 U.S.C. § 360b (2018).

110. *See* Guidance for Industry on Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs, *supra* note 17.

111. 21 U.S.C. § 321(v) (2018).

112. 21 U.S.C. § 321(g)(1)(C) (2018).

113. *See* Guidance for Industry on Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs, *supra* note 17.

114. *See, e.g.*, Ctr. for Food Safety, *supra* note 21; *cf.* Consumers Union, *supra* note 19.

115. 21 U.S.C. § 321(g)(1)(C) (2018); *see also* 21 U.S.C. § 321(g)(1), *supra* note 90 and accompanying texts.

Unquestionably, the altered genomic DNA affects the structure or function of the animal to obtain desirable traits; for example, the altered genomic DNA in the cattle transforms it into a hornless one.[116] Nevertheless, the altered genomic DNA is not an article. The FD&C Act does not define article and the FDA has pointed out that the term has a "broad meaning" throughout the FD & C Act.[117] The dictionary definition of "article" is "a thing or person of a . . . distinctive kind or class."[118] Distinctive means "separate or different."[119] Thus, an article must be separate and different from the recipient animal and therefore is "a necessary addition to induce a change to the structure or function of man or animal."[120]

Under certain circumstances, altered genomic DNAs using CRISPR-like technologies are not separate articles that are introduced into the recipient animal, but rather, products resulted from the cutting of Cas9 enzyme *in vivo*.[121] When using CRISPR-Cas9 to delete genetic material from the target cell, scientists introduce nothing new into the genome and the altered genomic DNA does not contain any foreign article that modifies the structure or function of the animal.[122] The FDA must distinguish this gene-editing process from a transgenesis process where a recombinant DNA construct is created externally outside an animal and then inserted into the animal's genome. With genome-edited animals, the targeted DNA sequences are part of the animal's genome, not a foreign addition, and the gene-editing process occurs completely *in vivo*, not *ex vivo*.[123] Therefore, the altered genomic DNA does not fit the definition of a drug under the FD & C Act because of the absence of an article as "a necessary addition" to the animal.[124]

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116. *See supra* Section I.B.

117. *See* 21 U.S.C. § 321 (2018); *see also* Pharmanex v. Shalala, 221 F.3d 1151, 1155 (10th Cir. 2000).

118. *Article*, MERRIAM-WEBSTER DICTIONARY (2019).

119. *Distinctive*, MERRIAM-WEBSTER DICTIONARY (2019).

120. Nat'l Milk Producers Fed'n, Comment Letter on The Food and Drug Administration's Draft Guidance for Industry #187 "Regulation of Intentionally Altered Genomic DNA in Animals" (June 19, 2017), https://www.regulations.gov/document?D=FDA-2008-D-0394-0413.

121. *See supra* section I.A.

122. *See* Nat'lMilk Producers Fed'n, *supra* note 121.

123. *See id.*

124. The conclusion of this section has limited implication on gene therapy using CRISPR-like technologies. Currently, the FDA regulates gene and cell

B. THE FDA'S GUIDANCE DEVIATES FROM THE CONVENTIONAL PRODUCT-BASED REGULATORY SCHEME SET FORTH IN THE COORDINATED FRAMEWORK.

Other than the legal flaws identified above, the FDA's guidance has not followed the policy set forth under the Coordinated Framework. The guidance deviates from the traditional product-based approach and focuses on the process that the animals are created by using CRISPR-like technologies instead.[125] It assumes that all gene-editing techniques are dangerous and "deemed unsafe" by construing altered genomic DNAs as new animal drugs.[126]

New gene-editing technologies like CRISPR-Cas9 underpin the inherent flaws of a process-based approach. First, animals created from gene-editing technologies impose less risk than those created from recombinant DNA technologies.[127] Currently, there is no scientifically objective method to distinguish animals created from conventional breeding methods from animals developed through use of gene-editing methods,[128] and sometimes conventionally bred animals pose more risk than

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therapy products under, among others, the Investigational New Drug Application. 21 C.F.R. § 312. When a cell is modified *ex vivo* for subsequent administration to humans, the cell can be construed as a drug under the FD & C Act. However, when the cell is altered *in vivo* using CRISPR-like technologies, no foreign article is inserted into the cell which cannot be construed as a drug itself. Regardless, the FDA has created expedited programs for regenerative medicine therapies that include human gene therapies, regardless how a cell is modified. *See generally* Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Draft Guidance for Industry, 82 FED. REG. 4825 (Feb. 19, 2019).

125. *See supra* note 73 and accompanying texts. *Cf*. James D. Murray & Elizabeth A. Maga, *Regulatory Dysfunction Inhibits the Development and Application of Transgenic Livestock for Use in Agriculture*, *in* ANIMAL BIOTECHNOLOGY 2: REPRODUCTIVE BIOTECHNOLOGIES 149, 157 (Heiner Niemann & Christine Wrenzycki eds., 2018) (finding that to date, worldwide governments have for the most part chosen to regulate the process of making a genetically engineered animal instead of the resulting product).

126. Regulation of Intentionally Altered Genomic DNA in Animals Draft Guidance, *supra* note 18.

127. *See* Section I.B.

128. The George Washington University Regulatory Studies Center, *supra* note 67, at 6; Jonas J. Monast, *Editing Nature: Reconceptualizing Biotechnology Governance*, 59 B. C. L. REV. 2377, 2399 (2018) (arguing that if CRISPR is analogous to selective breeding or natural selection, it follows that genome-edited organisms are no less natural than their counterparts that could foster similar genetic changes through conventional reproduction).

genome-edited animals.[129] Thus, under a process-based approach, genome-edited animals are subject to a similar or higher level of regulation than transgenic and conventionally bred animals even though genome-edited animals entail less risk of unintended changes to the genome.[130] An assumption of risk based solely on the use of a certain technique runs against the Coordinated Framework and can warrant regulatory oversight by the FDA.

Second, a process-based approach would stunt scientific development in gene-editing or other biotechnologies.[131] If pre-market oversight is imposed on all genome-edited animals using CRISPR-like techniques, only big corporations would be able to afford expensive and time-consuming health and environmental assessments while small companies would be unable to finance these costly safety assessments.[132] One might argue that only big corporations should be allowed to carry out biotechnology

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129. *See* George Washington University Regulatory Studies Center, *supra* note 67, at 6 (finding that random mutagenesis followed by phenotypic selection would result in more genome alterations).

130. *See* Alison Peck, *Re-Framing Biotechnology Regulation*, 72 FOOD & DRUG L. J. 314, 331–33 (2017) (finding that under a process-based approach, conventional breeding technologies would also fall under the scope of regulation); Pak, *supra* note 23 (discussing whether CRISPR-Cas9 is genetic engineering or a form of mutagenesis which is not subject to U.S. regulation); Kathleen M. Vogel, *Crispr Goes Global: A Snapshot of Rules, Policies, and Attitudes*, THE BULLETIN (June 5, 2018), https://thebulletin.org/2018/06/crispr-goes-global-a-snapshot-of-rules-policies-and-attitudes/ (finding that the EU court exempted crops created by gene-editing technologies from regulations because the result is nature-identical); s*ee also* Gregory Conko et al., *A Risk-based Approach to the Regulation of Genetically Engineered Organisms*, 34 NATURE BIOTECHNOLOGY 493 (2016) (finding that most regulatory regimes around the world do not follow the risk-based approach and that the degree of regulatory scrutiny in most cases is inversely proportional to the risk).

131. *See* Tomlinson, *supra* note 8, at 461 (quoting that the irony of subjecting groundbreaking scientific discoveries to an archaic regulatory scheme is causing many researchers to lose faith in the system); Marden & Kulkami, *supra* note 86 (exploring the impracticability of proposed regulatory changes that slow down development).

132. Rubin & Sax, *supra* note 72, at 596–97 ("Depending on how many agencies a firm may need to petition or voluntarily consult, the process currently requires ten years to bring a new GM product to market."); Jack Karsten & Darrell M. West, *New Biotech Regulations Require Balance of Safety and Innovation*, BROOKINGS (Mar. 3, 2017), https://www.brookings.edu/blog/techtank/2017/03/03/new-biotech-regulations-require-balance-of-safety-and-innovation/ (discussing concern for proposed regulations that could limit competition and innovation).

research because of their efficiency, economies of scale, and high standards of quality, but these advantages of big corporations seem ironic when CRISPR-like technologies democratize scientific applications and make gene-editing more accessible and economical.[133] The stringent process-based approach will likely push innovations to jurisdictions that provide a regulatory environment more hospitable to entrepreneurial activities and cause the U.S. to lose its competitive advantage in biotechnology fields.[134]

Third, a process-based regulatory approach would almost inevitably fall behind time and future development of biotechnology products.[135] Soon, there will be new technologies beyond CRISPR-Cas9 such as genomically recoded organisms created via synthetic DNA.[136] Agencies simply do not have the resources to develop new regulations in reaction to every new technology,[137] and a constantly changing regulatory landscape creates regulatory uncertainties that might stifle innovation.[138] In contrast, a product-based approach "specifies required outcomes or objectives rather than defining the way in which

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133. *See supra* section I.B.

134. Thierer, *supra* note 22 ("If policymakers erect more obstacles to innovation, it will encourage entrepreneurs to look elsewhere when considering the most hospitable place to undertake their innovative activities."); s*ee* Kevin Bryant, Ph.D., *Top 9 CRISPR Startup Companies Changing the Future of Biotech and Medicine*, SYNTHEGO, https://www.synthego.com/blog/crispr-startup-companies (last updated Jan. 3, 2019) (providing a list of startups applying CRISPR to various fields).

135. *See* NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 174 ("The profusion of future biotechnology products anticipated in coming years will challenge the federal agencies' ability to handle significant increases in the rate of biotechnology product innovation, the number of biotechnology products, the complexity of interactions, and the diversity of actors (and their experience with the regulatory process).").

136. *Id.* at 172.

137. For example, the FDA had to create new guidance documents from 2009 to 2017 in reaction to the emerging technologies like CRISPR-Cas9. William D. Eggers, Mike Turley & Pankaj Kishnani, *The Future of Regulation: Principles for Regulating Emerging Technologies*, DELOITTE INSIGHTS (June 19, 2018), https://www2.deloitte.com/insights/us/en/industry/public-sector/future-of-regulation/regulating-emerging-technology.html ("The policy cycle often takes anything from five to 20 years whereas a unicorn startup can develop into a company with global reach in a matter of months.").

138. *See also* Ann Bruce, *Novel GM Animal Technologies and Their Governance*, 22 TRANSGENIC RES. 681, 688 (2013) (arguing that regulatory uncertainty would also make it difficult for developers to assess the relative commercial advantage of the new technology and limit market innovation).

they must be achieved."[139] This approach is better at adapting to scaling modern innovations because the outcomes set by the regulators are unaffected by the development of new technologies.

Thus, when carrying out a benefit-risk assessment,[140] the FDA should have considered the risks of the product, the genome-edited animal, not the risks of the process, CRISPR-Cas9. It should have considered the effects of modified genetic material on the animal and whether food derived from the animal is safe for human consumption.[141] For the forgoing reasons, the FDA should ground its regulatory approach in the product-based approach identified in the Coordinated Framework.

C. WHEN FACING A SIMILAR SITUATION, THE USDA ADHERED TO THE PRODUCT-BASED APPROACH AND EXCLUDED GENOME-EDITED CROPS WITH CRISPR-LIKE TECHNOLOGIES FROM ITS JURISDICTION.

This Note recognizes that existing statutes and the current framework were not conceived to cover biotechnologies like CRISPR-Cas9. Nevertheless, it is not impossible to work with existing statutes while conforming to the Coordinated Framework. In 2016, the USDA had to determine whether it has the jurisdiction to regulate a type of CRISPR-edited anti-browning mushroom.[142] Under the USDA's regulation, a genetically engineered organism is deemed a regulated article "if it has been genetically engineered using a donor organism . . . that . . . meets the definition of a plant pest . . . ."[143] Unlike the FDA, the USDA determined that the genome-edited mushroom was beyond its regulatory authority because the "CRISPR/Cas9-edited white button

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139. Eggers, Turley & Kishnani, *supra* note 138.

140. *See* 21 U.S.C. § 355(d) (2018) (requiring a risk-benefit assessment framework).

141. *See* Nat'l Assn. of State Dep't of Agric., *supra* note 21 (arguing for these considerations).

142. *See* U.S. Dep't of Agric., Re: Request for Confirmation that Transgene-free, CRISPR-edited Mushroom Is Not a Regulated Article (Apr. 13, 2016) [hereinafter USDA Confirmation Request] https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf (assessing the potential regulation of the mushroom in question).

143. 7 C.F.R. § 340.1 (2019).

mushrooms . . . do not contain any introduced genetic material,"[144] and therefore, is not a regulated article.

Additionally, the USDA announced that it would not regulate crops that "could otherwise have been developed through traditional breeding techniques as long as they are not plant pests or developed using plant pests."[145] Genome-edited plants with CRISPR-like technologies could also be obtained through traditional breeding techniques as they do not contain artificially inserted genes from other species.[146] Therefore, they will not be overseen by the USDA. Compared to the FDA's approach, the USDA's approach towards genome-edited plants is much more nuanced, distinguishing genome-edited plants from genetically engineered plants by recombinant DNA techniques and adhering to the product-based approach outlined under the Coordinated Framework. The FDA could have adopted a similar approach towards genome-edited animals to encourage more beneficial innovations.

D. THE FDA SHOULD HAVE PROMULGATED RULES VIA NOTICE-AND-COMMENT PROCEDURE.

Lastly, the FDA could have promulgated a rule via the notice-and-comment process that would determine the circumstances under which genome-edited animals could be brought into the market, but it chose to issue a non-binding guidance document instead. The FDA defines guidance documents in its *Good Guidance Practices* (GGPs) as documents that "describe the agency's interpretation of or policy on a regulatory issue" and establish no "legally enforceable rights or responsibilities."[147] Yet, when the FDA interprets the new animal drug provisions under the FD&C Act to cover altered genomic DNAs, instead of making an interpretive rule, it is

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144. USDA Confirmation Request, *supra* note 143*; see also* Irus Braverman, *Editing the Environment: Emerging Issues in Genetics and the Law*, *in* GENE EDITING, LAW, AND THE ENVIRONMENT: LIFE BEYOND THE HUMAN 1, 7 (Irus Braverman ed., 2018) (discussing the USDA's decision regarding the mushroom).

145. Press Release, U.S. Dep't of Agric., Secretary Perdue Issues USDA Statement on Plant Breeding Innovation (Mar. 28, 2018), https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation ("With this approach, USDA seeks to allow innovation when there is no risk present.").

146. *See supra* section I.B.

147. 21 C.F.R. § 10.115 (2018).

actually making a legislative rule which imposes "a definitive obligation on a group of private persons."[148] Though the GGPs pronounces that a guidance document is not binding and affected parties may choose alternative approaches other than the one set forth in a guidance document,[149] the regulated parties would not "feel comfortable using anything other than the suggested form."[150]

Moreover, guidance documents afford little procedural safeguard to the public. The notice-and-comment process provides interested individuals with a meaningful opportunity to comment on the proposed rule through the submission of written "data, views, or arguments,"[151] of which significant comments must be incorporated into the final rule.[152] Affected individuals may challenge the rulemaking process on an arbitrary and capricious standard if the agency fails to consider public comments.[153] Guidance documents, however, are exempt from this requirement. Section 553 of the Administrative Procedure Act (APA) provides that "interpretative rules, general statements of policy, or rules of agency organization" are excluded from the notice-and-comment requirements, and administrative guidance falls under the exception of interpretative rules.[154] Instead of addressing all significant comments in the final rule, the FDA only needs to incorporate comments if it deems appropriate.[155] By resorting to issuing an administrative guidance, the FDA attempted to circumvent the increasing scrutiny the courts have devoted to notice-and-comment rulemaking.[156]

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148. Rubin & Sax, *supra* note 72, at 571.

149. *See* 21 C.F.R. § 10.115 (2018).

150. *See* Rubin & Sax, *supra* note 72, at 571–72 ("In legal doctrine or a law-school classroom, there may be a great difference between disobeying and annoying a government agency, but in the real, regulated world, that difference is not as evident.").

151. 5 U.S.C. § 553(c) (2018).

152. *See* Perez v. Mortg. Bankers Ass'n, 135 S. Ct. 1199, 1203 (2015) ("An agency must consider and respond to significant comments received during the period for public comment.").

153. *See* 5 U.S.C. § 706(2)(A) (2018) (invoking the arbitrary and capricious standard).

154. 5 U.S.C. § 553(b)(3)(A) (2018).

155. *See* 21 C.F.R. § 10.115 (2018).

156. Rubin & Sax, *supra* note 72, at 540–42, 566 (criticizing guidance as an improper attempt of rulemaking and one of the most controversial techniques in administrative law).

Notably, one might argue that by issuing a guidance document which is a soft law mechanism, agencies can now adapt quickly to changes in technology and address issues as they arise without stifling innovation.[157] However, when regulated products might potentially pose unknown risks to the environment and human health, the regulation should, at least, provide a basis for a legal challenge and thus allow for judicial review.[158] The public needs an avenue to understand genome-edited products and thereby "reduc[e] irrational fears about [their] safety," and small firms need an avenue to promote the benefits they could offer to the public and the market, "or at least compel the [a]gency to defend the burdens it imposes on these firms."[159] Thus, a guidance document which does not confer the public with a sufficient participatory mechanism is not the best tool to deal with genome-edited products and the FDA should have issued a rule through the informal rulemaking process under the APA.

The FDA's guidance #187 faces so many legal, procedural, and policy challenges that the agency must come up with a new regulatory approach towards genome-edited animals with CRISPR-like techniques. If the FDA were to find that it lacks any authority to extend its jurisdiction over genome-edited animals, other agencies might be able to fill in this gap.

III. POLICY CONSIDERATIONS MOVING FORWARD

The analysis above has identified a few gaps within the current regulatory structures, which were not created to regulate genome-edited animals with emerging biotechnologies. Therefore, with these pitfalls of the FDA's draft guidance, this Part proposes several alternative pathways to regulate genome-edited animals with CRISPR-like technologies. Additionally, under the current Coordinated Framework, agencies follow a product- and risk-based approach to regulate genome-edited

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157. *See* William McGeveran, *Friending the Privacy Regulators*, 58 ARIZ. L. R. 959, 987 (2016) (explaining how flexible regulation can help regulators remain responsive to rapid technological change).

158. *Cf.* Rubin & Sax, *supra* note 72, at 587 (highlighting the weakness in the Coordinated Framework used to regulate genetically modified food because, as an administrative guidance, and thus a planning document, it provided no basis for a legal challenge or judicial review).

159. *Id.* at 599.

animals.[160] However, a traditional risk-based approach faces limitations in the context of new biotechnologies such as CRISPR-Cas9 when the risks associated are uncertain and ambiguous. Thus, there is an urgent need for the White House to creates a framework with a single point of entry to regulate genome-edited products, and update the Coordinate Framework to incorporate the Responsible Research and Innovation (RRI) principles to balance precaution and innovation, process and product, as well as interests of developers and the public.

A. REGULATORY GAP AND ALTERNATIVE REGULATORY PATHWAYS FOR GENOME-EDITED ANIMALS WITH CRISPR-LIKE TECHNOLOGIES UNDER EXISTING STATUTES

Although the FDA's updated guidance has many controversial aspects of regulating genome-edited animals, it indicates the agency's attempt to fill in the gap of agency jurisdiction under the Coordinated Framework. Were the FDA to find that it lacks the jurisdiction to cover genome-edited animals under existing statutes, letting them fall completely outside of oversight, like how the anti-browning mushroom fell outside of the USDA's jurisdiction, it might not be an assuring idea for the public at large.[161]

The FDA no longer has to be the lead agency exercising oversight of animals for human use after the 2017 update to the Coordinate Framework which encouraged agencies to coordinate amongst each other.[162] Therefore, federal agencies might explore alternative pathways to exercise oversight of genome-edited animals with CRISPR-like technologies.[163] One possible solution

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160. *See* WHITE HOUSE, *supra* note 69, at 8 ("Exercise of agency oversight within the scope afforded by statutes should be commensurate with the risk posed by the introduction of the biotechnology product and should not turn on the fact that it was created or has been altered by a particular process or technique.").

161. *See* Mark Shwartz, *Target, Delete, Repair*, STAN. MED., https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html (last visited Mar. 26, 2019) ("When it comes to experiments on animals, . . . two things worry me . . . . One is the intentional misuse of CRISPR. The other is that people with good intentions will inadvertently cause harm.") (citing Stanford bioethicist Hank Greely, JD).

162. *See* WHITE HOUSE, *supra* note 69, at 29.

163. The FDA could still exercise oversight of genome-edited animals if they are used to create new human drugs and biological products; the USDA could continue regulating genome-edited animals as animal pests that transmit

for the agencies, a solution that has not been explored at all, is to regulate the construct inserted into the targeted animal—the guide RNA and the Cas9 protein—instead of the altered genomic DNA.

i. New Animal Drug under the FD&C Act

Although the altered genomic DNA is not a drug, the FDA might, one day, regulate the guide-RNA/Cas9 construct inserted into the targeted animal as a new animal drug.[164] The key question to determine is whether this construct constitutes a drug or medical device. Under the FD&C Act, a medical device is an article that is "intended to affect the structure or any function of the body of man or other animals" and "does not achieve its primary intended purposes through chemical action."[165] When the construct is inserted into the targeted cell, Cas9 binds specifically to the targeted DNA and cleaves the two DNA strands to get rid of particular genetic material.[166] It is generally acknowledged among scientists that when Cas9 cleaves the DNA strands, it is catalyzing the splitting of the chemical bonds in the strands.[167] If the DNA cleavage is characterized as a chemical action, then the construct will likely be a new animal drug; otherwise, the construct will likely be a medical device.

The interpretation of the term "chemical action" is a nuanced one that the FDA and the scientific community constantly grapple with.[168] The FDA clarified in the guidance that "a product that exhibits . . . intermolecular forces does not

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diseases. For regulatory purposes, genome-edited animals are not distinguishable from other animals. *See supra* section I.F.

164. The FDA is charged with protecting the public health by ensuring that animal drugs are safe and effective. 21 U.S.C. § 393(b)(2)(B) (2018).

165. 21 U.S.C. § 321(h)(3) (2018).

166. *See* GALLO ET AL., *supra* note 10, at 2–3 (explaining how the CRISPR-Cas9 system functions).

167. *See, e.g.*, Cong Huai et al., *Structural Insights into DNA Cleavage Activation of CRISPR-Cas9 System*, NATURE COMM. 2 (Nov. 9, 2017), https://www.nature.com/articles/s41467-017-01496-2 ("[T]hen, the two nuclease domains (HNH and RuvC) catalyze the splitting of the scissile [covalent chemical] bonds in two DNA strands, respectively.").

168. *See* Classification of Products as Drugs and Devices and Additional Product Classification Issues, 82 FED. REG. 44802, 44803 (Sept. 26, 2017) (explaining how following public comments the FDA revised the guidance to more clearly explain the agency's thinking regarding the interpretation of "chemical action.").

exhibit 'chemical action' under section 210(h) unless the product . . . mediates a bodily response at the cellular or molecular level . . . ."[169] The guidance also illustrates that a catalyst interacts with the body through intermolecular forces and "mediates a bodily response at the cellular or molecular level by catalyzing a number of enzymatic reactions of the body . . . ."[170] Similar to the catalyst example, when Cas9 binds to the targeted DNA and cleaves the strands, it interacts with the strands through intermolecular forces and triggers the cell to repair the damage by such cleavage.[171] Therefore, it is likely that the DNA cleavage exhibits chemical action and thus, the guide-RNA/Cas9 construct is not a medical device, but a drug under the FD & C Act.

ii. Veterinary Biologic under the Virus-Serum-Toxin Act (VSTA)

Alternatively, the USDA might be able to construe the guide-RNA/Cas9 construct as a veterinary biologic and thus regulate it under the VSTA.[172] Veterinary biologics are "products derived from living organisms and biological processes" that are "used to prevent, diagnose, or treat animal diseases."[173] The USDA must approve a veterinary biologic to be "pure, safe, potent, and efficacious" before it is introduced into the market.[174] Currently, scientists have succeeded in disrupting the prion gene that can cause the mad cow disease with CRISPR-Cas9 to

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169. FOOD & DRUG ADMIN., GUIDANCE FOR THE INDUSTRY AND FDA STAFF: INTERPRETATION OF THE TERM 'CHEMICAL ACTION' IN THE DEFINITION OF DEVICE UNDER SECTION 201(H) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 3 (2017), available at https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Gray%20Sheet/38/40/chemical_action_guidance.pdf (distributing a draft guidance for comment purposes only).

170. *Id.*

171. *See* Univ. of Cal. Berkeley, *supra* note 39.

172. *See generally* 21 U.S.C. §§ 151–159 (2018) (conferring authority for the Secretary of Agriculture to regulate "any virus, serum, toxin, or analogous product for use in the treatment of domestic animals.").

173. U.S. DEP'T AGRIC., PROGRAM AID NO. 1713, VETERINARY BIOLOGICS: USE AND REGULATION 1 (2013). The statute does not define the term "veterinary biologic." *See* 21 C.F.R. § 510.3 (listing definitions).

174. *Common Questions About Veterinary Biologics*, U.S. DEP'T OF AGRIC., https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/ct_vb_pel_faqs (last modified July 17, 2015).

prevent cattle from contracting the disease.[175] In this case, the guide-RNA/Cas9 construct can be construed as a veterinary biologic that prevents animal diseases in cattle by knocking out the responsible gene, since the USDA already licensed the first veterinary RNA vaccine in 2012.[176] As such, the USDA might be able to regulate the guide-RNA/Cas9 construct as a veterinary biologic.

iii. Pesticide Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

Lastly, the EPA might be able to construe the guide-RNA/Cas9 construct as a pesticide and thus regulate it under the FIFRA.[177] Pesticide means any substance "intended for preventing, destroying, repelling, or mitigating any pest."[178] In the United States, genetically engineered insects have already been released into the environment—Oxitec mosquitoes that combat Zika—and have been regulated as a pesticide by the EPA because they are intended to reduce the population of mosquitoes in future generations and bring the species to its extinction.[179] Recently, scientists have succeeded in using CRISPR-Cas9 to wipe out a type of mosquito "in as few as seven

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175. *See* THE NETH. COMM'N ON GENETIC MODIFICATION, CRISPR & ANIMALS: IMPLICATIONS OF GENOME EDITING FOR POLICY AND SOCIETY 34 (2018); *see also* Helen Briggs, *'Tuberculosis-resistant' Cattle Developed in China*, BBC (Feb. 1, 2017), https://www.bbc.com/news/science-environment-38810073 (reporting tuberculosis-resistant cattle has been created using the CRISPR-Cas9 system).

176. U.S. DEP'T OF AGRIC., *supra* note 173, at 9; *see also New Swine Flu Vaccine Licensed*, NAT'L HOG FARMER (Oct. 8, 2012), https://www.nationalhogfarmer.com/health/new-swine-flu-vaccine-licensed (reporting that the USDA approved a swine influenza virus H3N2 vaccine that utilizes RNA Particle Technology).

177. The EPA is charged with protecting human health and the environment by ensuring registered pesticide products result in no unreasonable adverse effects to man or the environment. 7 U.S.C. § 136a(c)(5) (2018).

178. 7 U.S.C.§ 136(u) (2018).

179. *See* U.S. FOOD & DRUG ADMIN., CLARIFICATION OF FDA AND EPA JURISDICTION OVER MOSQUITO-RELATED PRODUCTS: GUIDANCE FOR INDUSTRY 6 (2017) (clarifying the regulatory role the EPA shares in gene edited mosquitos); Andrew Hammond, *Here's the Plan to End Malaria with CRISPR-edited Mosquitoes*, WIRED (Sept. 24, 2018), https://www.wired.com/story/heres-the-plan-to-end-malaria-with-crispr-edited-mosquitoes/ (explaining how genetically modified sterile mosquitos were released into the wild to combat Zika in America).

generations."[180] In this case, the guide-RNA/Cas9 construct inserted into the mosquito genome, together with the resulted mosquito, functions as a pesticide that annihilates the mosquito population, making it subject to the EPA's jurisdiction.[181] Future pesticide-like genome-edited animals might also be subject to this regulatory pathway instead of being regulated by the FDA.

Although these agencies might be vested with the statutory authority to exercise oversight of the guide-RNA/Cas9 construct, it might not be a sound policy for them to do so because regulating the construct in this way would focus purely on the process, running counter to the product-based approached laid out under the Coordinated Framework.[182] Additionally, with the constant change in technologies, regulations cannot be grounded in a particular process but must stay flexible to remain relevant and effective.[183] As such, the White House must set up a new framework to facilitate the agencies to determine the fine balance between encouraging innovation and rendering oversight of new technologies.

B. THE WHITE HOUSE SHALL UPDATE THE COORDINATED FRAMEWORK WITH THE RRI PRINCIPLES THAT BALANCES PRECAUTION AND INNOVATION POTENTIAL OF GENOME-EDITED PRODUCTS

i. Limitations of a Risk-Based Approach towards Genome-Edited Products

The Coordinated Framework has adopted a risk-based approach towards biotechnological products.[184] As explained in the section above, a risk-based approach assesses risks based on characteristics of the organism, the target environment, and the

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180. Hammond, *supra* note 179.

181. *See* U.S. FOOD & DRUG ADMIN., *supra* note 179.

182. *See* discussions *supra* section II.A.ii.

183. *See* NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 93–99 ("[A]lthough the products of future biotechnology are often likely to be within the jurisdiction of existing regulators, they may struggle to regulate these products effectively and to respond nimbly to the products that will be coming."); Meagan Davis, The Proper Regulation and the Use of CRISPR/Cas9 in the 21st Century 14 (Apr. 2018) (unpublished student essay) (on file with the College of Saint Benedict/Saint John's University) ("With the constant change of technology, regulations need flexibility and stability to stay relevant and effective").

184. *See* Meghani, *supra* note 73 and accompanying texts.

type of application.[185] Currently, the quantitative risk assessment is widely used for new biotechnological products, which means that the risk of the new organism on the ecologic environment and human health is quantified by measurable, objective data.[186]

However, a risk-based assessment works best only when the risks are "clearly defined and quantifiable."[187] Risks of genome-edited animals with emerging biotechnologies like CRISPR-Cas9 are uncertain, ambiguous, and unfamiliar because of their "inherent fluid boundaries, possible fields of application, and the unknown and extremely dynamic future developments."[188] Currently, there is no sufficient baseline of information to accurately assess the risks of products created with new technologies.[189] Thus, a risk-based approach is handicapped when the risks of genome-edited products cannot be quantified and evaluated against their benefits.

ii. Moving toward RRI to Address Risks While Fostering Public-Welfare-Oriented Responsible Innovation

Given the unique nature of CRISPR-like technologies and the likelihood of having future biotechnologies that no one could have foreseen, U.S. agencies should move towards an approach that finds the right balance between precaution and innovation.[190] On the one hand, regulators should be wary of the unknown risks associated with genome-edited products on the environment, human health, and safety. On the other hand, regulatory agencies cannot inhibit innovation.[191] Future regulation will need to balance the dynamic relationships of "the nature of the innovative products developed, their areas of

185. *See* WHITE HOUSE, *supra* note 69 and accompanying texts.

186. NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 150.

187. *See* Matthias Braun & Peter Dabrock, *Mind the Gaps!*, EMBO REPORTS (Dec. 27, 2017), http://embor.embopress.org/content/early/2017/12/27/embr.201745542.

188. *Id*.

189. NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 152.

190. Nina Duensing et al., *Novel Features and Considerations for ERA and Regulation of Crops Produced by Genome Editing*, FRONTIERS IN BIOENGINEERING & BIOTECHNOLOGY , June 2018, at 14, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6016284/pdf/fbioe-06-00079.pdf.

191. *See* Braun & Dabrock, *supra* note 197.

application, and the time-scales for their development."[192] When in doubt, responsible governance demands the agencies "give precedence to the protection of human dignity, human health or the environment, rather than to organizational or economic interests."[193]

With these principles in mind, the White House could update the Coordinated Framework with the RRI principles and move towards a participatory approach that allows the agencies to work with all societal actors during the innovation process and to bring out new technologies that are reconciled with societal values, needs, and expectations.[194] Philosopher and Scientist René von Schomberg notes that:

Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society).[195]

A risk-based approach often values expert knowledge and authority. With public participation, regulators have better knowledge of what laypeople consider important and what innovations might be acceptable and socially desirable.[196] Rather than hindering a potentially risky product from being marketed, RRI promotes the continuous involvement of various stakeholders and considers various perspectives so that a

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192. Bruce, *supra* note 139, at 690. *See also* Williams, *supra* note 74, at 458 (arguing that regulatory review must "balance the interest of the public, the affected organism, and the environment.").

193. Braun & Dabrock, *supra* note 197.

194. *See* EURO. COMM'N., *Responsible Research & Innovation* (last visited Mar. 8, 2019), https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation ("RRI implies that societal actors (researchers, citizens, policy makers, business, third sector organizations, etc.) work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society.").

195. René von Schomberg, *A Vision of Responsible Research and Innovation*, *in* RESPONSIBLE INNOVATION: MANAGING THE RESPONSIBLE EMERGENCE OF SCIENCE AND INNOVATION IN SOCIETY 51, 63 (Richard Owen et al. ed., 2013).

196. *See* Alexander Bogner & Helge Torgersen, *Precaution, Responsible Innovation and Beyond – In Search of a Sustainable Agricultural Biotechnology Policy*, FRONTIERS IN PLANT SCI. (Dec. 18, 2018), https://www.frontiersin.org/articles/10.3389/fpls.2018.01884/full#note3.

product can be better aligned with societal expectations.[197] Under this framework, regulators are able to address the risks of new products in the context of the acceptability of their applications and to promote public welfare-oriented responsible innovation.

iii. Adopting RRI to Regulate Genome-Edited Animals Using CRISPR-Like Technologies

Applying the approach that balances precaution and innovation to regulate genome-edited animals, the FDA and other agencies could evaluate the risks of the use of CRISPR-Cas9 or other similar technologies in their applications, gather inputs from the public regarding their acceptability of the product applications, and work collaboratively with developers to develop rules that will be aligned with public values and expectations. For instance, the FDA might attach conditions to approval of new genome-edited animals into the market to ensure that the environmental and social benefits outweigh harms.[198] The FDA could even provide more carrots to incentivize innovation that would improve animal welfare, environmental, and social benefit—like the hornless breed of cattle produced by Recombinetics.[199]

Remarkably, on October 30, 2018, the FDA announced a new program, the Veterinary Innovation Program (VIP), incentivizing animal biotechnological advancement while ensuring the safety of animal products.[200] Developers of certain intentionally altered animals using genome-edited technologies that "provide a benefit to human health, animal health, animal well-being, or enhanced food production" may participate in the

197. *Id*.

198. For instance, in Denmark genetic modification of animals is "restricted to applications benefitting human health and the environment." *See* Bruce, *supra* note 47, at 391. In the Netherlands, "genetic modification of animals for food purposes needs a license requiring the product to serve a public interest and have no overriding ethical objections. *Id*."

199. *Id*.

200. U.S. FOOD & DRUG ADMIN., CTR. FOR VETERINARY MED., *FDA Announces Plant and Animal Biotechnology Innovation Action Plan*, U.S. FOOD & DRUG ADMIN. (updated Nov. 29, 2018), https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm624490.htm.

VIP.[201] Eligible developers will have the opportunity to interact with the Center for Veterinary Medicine review team, receive hands-on assistance throughout the review process, and obtain additional review process benefits such as alternative data options.[202] This collaboration between the agency and developers can increase the predictability of the regulatory pathway, facilitate a lower number of review cycles, and reduce the overall time for approval.[203] Indeed, the groundbreaking VIP is an example of the FDA moving towards a participatory approach regulating new biotechnology products. Through eliciting public response, working with developers who promote public welfare with biotechnologies, and assisting developers in managing the risks of their product applications at an earlier stage, the FDA is better able to align public values and needs, facilitate innovation, and create a targeted, flexible review framework for genome-edited animals.

iv. Setting up a Single Point of Entry

Coupled with adopting the RRI principles, the White House could also update the Coordinated Framework with a "single point of entry" for product developers. The National Academies of Sciences, Engineering, Medicine proposes in its report the following framework:

Potential product developers and interested parties would begin by going to an entry point and providing characteristics of the intended product and its use pattern. If the product does not fall under a federal statute, the developer would be notified that the product is not federally regulated. If the product is regulated, the appropriate agency or agencies would be identified for the developer. An evaluation of the product's familiarity to

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201. U.S. FOOD & DRUG ADMIN., *VIP: Veterinary Innovation Program for Certain New Animal Drug Applications for Intentionally Altered Genomic DNA in Animals and Animal Cell, Tissues, and Cell- or Tissue-Based Products* (updated Oct. 30, 2018), https://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/BiotechnologyProductsatCVMAnimalsandAnimalFood/AnimalswithIntentionalGenomicAlterations/ucm620835.htm.

202. *Id.*

203. *Id.* The FDA plans to publish guidance documents this year to clarify its intended oversight processes and clear criteria and data requirements in evaluating new animal biotechnology products. *See* Jay Sjerven, *F.D.A. Unveils Plan to Help Guide Innovation in Biotechnology*, FOOD BUS. NEWS (Nov. 7, 2018), https://www.foodbusinessnews.net/articles/12835-fda-unveils-plan-to-help-guide-innovation-in-biotechnology.

regulatory agencies and its complexity in terms of risk analyses as compared to existing biotechnology products would be ascertained []. Depending on the product's familiarity and the complexity of its risk analysis, a different set of risk-analysis processes would be employed . . . .[204]

Under a single point of entry, developers can "evaluate whether the intended use of the product is regulated under a given statute" instead of window-shopping for regulatory approval from different agencies.[205] A new office could also be set up to facilitate inter-agency consultations where the risks of a new product are uncertain and to set future regulatory directions for biotechnologies.[206] This framework would provide an "accessible public face for the regulatory system" for product developers, add certainty to the current regulatory system, and ensure no new products fall outside of the regulatory framework.[207]

CONCLUSION

Existing regulatory structures for genome-edited products with technologies like CRISPR-Cas9 cannot keep up with the development of biotechnologies. A case in point is the FDA's guidance #187 that attempts to extend its jurisdiction of genome-edited animals to intentionally altered genomic DNAs, although existing statues do not allow it to do so. The FDA erroneously interpreted genomic DNA edited with CRISPR-like technologies as a new animal drug under the FD & C Act, which was not conceived to cover genome-altered animals when it was first passed by Congress. The FDA overlooked the product- and risk-based approach set under the current Coordinated Framework and adopted a process-based approach that opposes the regulatory and scientific consensus. The FDA also circumvented the notice-and-comment rulemaking process by

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204. NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 9.

205. *Id.* at 142, 174–75 ("To enable effective regulation of the safe use of future biotechnology products, it would be beneficial to have a single point of entry into the regulatory system with a decision-making structure aimed to assess and manage product risk, to direct products to their appropriate regulatory agencies, and to increase transparency for developers and society.").

206. *See* Peck, *supra* note131, at 335–36 ("[T]he office would serve as a resource for the regulators and the public by monitoring and compiling information about approvals . . . agency procedures, and inter-agency consultations.").

207. NAT'L ACAD. OF SCI., ENG'G, AND MED., *supra* note 68, at 141–43.

instead issuing a guidance document exempted from the APA procedural requirements, despite its practically binding legal effects. Consequently, this guidance has made the future regulatory landscape regarding genome-edited animals uncertain and could potentially stifle public confidence and scientific innovation that would bring benefits to the environment and human health. Though agencies may construe the guide-RNA/Cas9 construct inserted into the animal's genome as a new animal drug, a veterinary biologic, or a pesticide and extend their oversight of the construct under relevant existing statutes, the current structure will handicap future biotechnology development.

More could be done, and a new regulatory approach must be introduced. The White House should update the Coordinated Framework with a "single point of entry" and encourage the agencies to move towards RRI that fosters responsible innovation which aligns with public values and expectations. The FDA's proposed VIP is an illustration that an agency could move towards a more cautious, nuanced direction when facing the unknown and towards a participatory framework that balances innovation, oversight, and public interest.

Last but not least, regulatory agencies must have open communication with the public. More open debates are needed to clarify policy objectives regarding new biotechnologies. The public should be able to participate in discussions that determine what constitutes harm, what level of risk is acceptable, and who should bear the risk. Agencies must ensure that they gather information from all interested parties and incorporate their opinions into the respective rulemaking processes. Most importantly, agency rules must articulate clear standards for any regulatory approach, providing certainty for the public and developers of new technologies.

What is the right regulatory approach towards emerging biotechnologies? RRI might be a solution, but the inquiry should not stop there. CRISPR-Cas9 democratizes scientific advancement, and regulation should not be the impediment to scientific progress. While some level of oversight is required, the bottom line is that we need the right amount of regulation and an approach towards CRISPR-like technologies that will keep genome research vibrant, maintain the U.S. competitive edge and leadership position, and ensure our present citizens can receive the benefits that CRISPR-like technologies provide.