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CRISPR: Redefining GMOs—One Edit at a Time

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CRISPR: REDEFINING GMOS—ONE EDIT AT A TIME

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I. INTRODUCTION

Genetically modified organisms (GMOs) are the center of some of the most polarizing beliefs in today's society. Certain individuals view GMOs as long-sought solutions to some of the world's biggest problems, from recycling materials to fueling transportation to feeding the growing human population. Other groups, however, believe that GMOs are a threat to the natural world. These groups offer warnings, including the uncertainties resulting from processing and modifying natural products, as well as the indeterminate long-term effects of making such changes. Although divergent in beliefs, both groups passionately argue their views online, in government forums, and in the scientific press.

Herbert Boyer and Stanley Cohen are credited with the formulation of the first GMO – bacteria that was genetically modified to include a gene from another bacterium.[1] In 1973, Boyer and Cohen inserted a particular gene from a bacterium into a plasmid.[2] They then induced uptake of the plasmid by a different bacterium.[3] The result was a modified bacterium with a novel gene that provided resistance to the antibiotic kanamycin, a property conferred by the gene from the original bacterium.[4]

From these humble beginnings, the biotechnology community formed around GMOs has grown by leaps and bounds. The science behind GMOs has evolved at a breakneck pace, thanks to advances made by recombinant bacteria, by Polymerase Chain Reaction (PCR), and by transgenic plants. However, perhaps the biggest scientific discovery of an entire generation, CRISPR, offers the unique opportunity to rewrite the definition of GMOs as they are known today.

CRISPR, an acronym for Clustered Regularly Interspaced Short Palindromic Repeats, is a novel gene editing technology that has been called one

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1. *Genetics and Genomics Timeline*, GENOME NEWS NETWORK, http://www.genomenewsnetwork.org/resources/timeline/1973_Boyer.php (last visited Mar. 5, 2017).
2. *Id.*
3. *Id.*
4. *Id.*

of the greatest scientific discoveries in the last century.[5] The CRISPR system, also known as the "CRISPR-Cas9" system, is a simple and inexpensive method to identify an "unhealthy" genetic sequence in an organism, cut the sequence out, and then replace the removed "unhealthy" sequence with a "healthy" version.[6] This amazing process results in an organism with a corrected genetic sequence that, importantly, is made up entirely of its own native genes.[7]

The fact that the CRISPR system can use an organism's own genetic library to correct damaged DNA results in a far different outcome than some methods that have been historically used to create GMOs.[8] Using CRISPR in this capacity, the corrected genetic system is not a "hybrid" mishmash of DNA obtained from different organisms. Instead, the corrected DNA in a CRISPR-modified organism comes from the organism itself.[9] In other words, although an organism does in fact undergo genetic editing using CRISPR, the resulting CRISPR-modified organism is indistinguishable from a normal organism in nature that is free of the ailment that was fixed by the CRISPR process.[10]

In particular, the agricultural community is struggling to understand how the CRISPR system will affect current procedures, processes, and products. In this regard, Maywa Montenegro, a food systems researcher and a PhD candidate in Environmental Science, Policy and Management at the University of California, Berkeley, may have said it best:

> CRISPR is giving us a rare opportunity, then, to escape GMO definitions stuck in the 1980s and begin treating agriculture and food as the complex systems they are. It invites us to update biotech governance to include expertise from a wider public and range of sciences. We'll need to consult not just geneticists but also ecologists. Not just natural scientists but social scientists. Not just scientists, but farmers, consumers, seed producers and workers across the food chain.[11]

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5. *See* Antonio Regalado, *Who Owns the Biggest Biotech Discovery of the Century?*, MIT TECH. REV. (Dec. 4, 2014), https://www.technologyreview.com/s/532796/who-owns-the-biggest-biotech-discovery-of-the-century/.

6. *Id*.

7. *Id.*

8. *Id.*

9. *Id.*

10. Institute for Basic Science, *Genome-edited Plants, Without DNA: CRIPSR-Cas9 RNP Technique in Plants Could Be the Key to Feeding the Planet,* SCI. DAILY (Oct. 19, 2015), https://www.sciencedaily.com/releases/2015/10/151019123744.htm.

11. Maywa Montenegro, *CRISPR is Coming to Agriculture – with Big Implications for Food, Farmers, Consumers and Nature*, ENSIA (Jan. 28, 2016), https://ensia.com/voices/crispr-is-coming-to-agriculture-with-big-implications-for-food-farmers-consumers-and-nature/.

In summary, CRISPR is a game changer for defining what is and what is not a genetically modified organism. Part II of this paper will explain the science of using the CRISPR system as a genetic editing tool.[12] Part III will explore the current and potential applications of CRISPR in humans, animals, and plants.[13] Part IV will summarize the important battle over the inventorship of the CRISPR process that will ultimately determine the true owner of the technology.[14] Finally, Part V of this article will examine the growing regulatory quandary faced by various countries on how to classify organisms modified by CRISPR.[15]

II. DEFINING THE CRISPR SYSTEM AND ITS USE AS A GENETIC EDITING TOOL

Modifying organisms via genetic manipulation has been the foundation of biotechnology research for several decades.[16] For most organisms, deoxyribonucleic acid (DNA) is the main genetic material and is made of nucleotide bases adenosine (A), thymidine (T), cytidine (C), and guanosine (G).[17] Nearly all advances in biotechnology research and innovation are developed from this basic framework.

In 1984, CRISPR was first identified during a study of the bacterial genome.[18] CRISPR is represented by short DNA sequences followed by the same DNA sequence in reverse, also known as the "palindromic sequence."[19] This is followed by about thirty base pairs of DNA, known as "spacer" DNA, which then is followed by a repeat of the palindromic sequence.[20] These DNA sequences represent a significant portion of the bacterial genome and almost all archaea, a domain and kingdom of single-celled microorganisms.[21] For many years, the scientific community assumed that these sequences were nothing more than "junk" DNA due to the frequency

12. *See infra* Part II.
13. *See infra* Part III.
14. *See infra* Part IV.
15. *See infra* Part V.
16. *See, e.g.*, Asude Alpman Durmaz et al., *Evolution of Genetic Techniques: Past, Present, and Beyond*, BIOMED RES. INT'L 1, 1 (2014).
17. U.S. National Library of Medicine, *What Is DNA?*, GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/primer/basics/dn https://ghr.nlm.nih.gov/primer/basics/dna (last visited Dec. 19, 2017).
18. Michael J. Stern et al., *Repetitive Extragenic Palindromic Sequences: A Major Component of the Bacterial Genome*, 37 CELL 1015, 1015 (1984) (the conserved nucleotide sequence identified as the REP (repetitive extragenic palindromic) sequence in *E. coli* and *S. typhimurium* is now recognized as the first description of the machinery now known as CRISPR technology).
19. Elizabeth E. Pennisi, *The CRISPR Craze*, 341 SCI. 833, 834 (2013).
20. Stern et al., *supra* note 18, at 1015.
21. *Id.*

of seemingly unimportant repetition in the sequences.[22] This assumption, however, fell by the wayside as more and more genomic information became available to scientists in the 1990s and 2000s.[23]

In 2005, researchers discovered that the spacer DNA sequences in the bacterial genome actually matched the DNA sequences known to be present in viruses.[24] This breakthrough indicated that that the spacer DNA sequences may not be junk DNA after all and ultimately suggested a role in microbial immunity.[25] Bacteria are commonly infected by viruses, so scientists hypothesized that bacteria may actually integrate the viral DNA into their own DNA as a sort of defense mechanism to quickly identify and disable viruses upon infection.[26] In other words, bacteria appeared to be able to take up invading viral DNA and make it part of the bacteria's own genetic code to form a sort of "catalog" of viral DNA. If a virus infects the bacteria in the future, the bacteria can reference the catalog of viral DNA and readily identify the virus as an invading, non-bacterial organism.

Dr. Jennifer A. Doudna, a researcher at the University of California, Berkeley, discovered how bacteria utilize CRISPR spacer DNA (crDNA) as a defense mechanism.[27] Bacteria use a single-sided section of crDNA (crRNA) as a guide mechanism, in tandem with an enzyme known as Cas9, to identify a virus that had invaded the bacteria.[28] Cas9 is an enzyme that cuts the identified viral DNA at the end of the crRNA complementary sequence, thus inactivating the virus.[29] This simple mechanism is very effective at identifying specific genetic sequences and quickly inactivating them to prevent damage. Essentially, the Cas9 enzyme cuts the DNA like scissors, and CRISPR is the guide mechanism that tells Cas9 where to cut.

After realizing the power of CRISPR as a defense system in organisms, scientists began working on how to adapt the process as a genetic editing tool.[30] Dr. Doudna and her team modified the system to create a single guide RNA (sgRNA) that could include *any* RNA sequence to direct the Cas9 pro-

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22. *Id.* (due to the repetitive nature of REP sequences, it was assumed that DNA only reflected nonsense "junk" sequences in the genome).

23. *See* Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG. (Feb. 6, 2015), https://www.quantamagazine.org/20150206-CRISPR-dna-editor-bacteria.

24. *Id.*

25. *Id.*

26. *Id.*

27. *See* Dipali G. Sashital et al., *Mechanism of Foreign DNA Selection in a Bacterial Adaptive Immune System*, 46 MOLECULAR CELL 606, 606 (2012).

28. Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 1258096-1, 1258096-2-1258096-3, 1258096-5 fig. 4 (2014).

29. *Id*. at 1258096-2.

30. *Id*. at 1258096-1to -5.

tein to cut DNA at a specific point.[31] The innovative aspect of the CRISPR-Cas9 system is that it uses a RNA-based recognition of DNA instead of a protein-based recognition.[32] The result is that the CRISPR-Cas9 system is more effective and simpler than having to produce an individual protein for every desired genetic cleavage, which had been the gold standard in the genetic world.[33]

Scientists developed several competing genetic-editing technologies before CRISPR, including meganucleases,[34] zinc finger nucleases (ZFNs),[35] and transcription activator-like effector nucleases (TALENs).[36] However, CRISPR is seen to be advantageous over the competing systems due to its accessibility, its inexpensive cost, and the ease with which it can be made and used.

To utilize the CRISPR system, scientists first create a CRISPR "guide" molecule that matches a specific DNA sequence of interest.[37] In this regard, CRISPR is used as a kind of GPS device to find its intended target on the DNA double helix where genetic editing is desired.[38] Once it arrives at the precise position in the DNA, CRISPR cuts and splices the DNA with Cas9 enzyme in order to remove the sequence from the genome.[39] The CRISPR system then incorporates a corrected sequence into the genome provided by scientists to "fix" the cut DNA sequence.

As discussed in Part III of this paper, the CRISPR-Cas9 process has been harnessed into a powerful system that can edit specific sites of DNA in virtually any organism.[40] Genetic modifications using CRISPR can be used to activate, add, delete, or suppress genes.[41] In this way, CRISPR acts as a sort of "cut and paste" mechanism for genetic content within targeted regions of an organism's genome. At this early stage of development, the possibilities for CRISPR appear to be nearly endless.

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31. Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 819–20 (2012).

32. *Id.*

33. Pennisi, *supra* note 19, at 835.

34. Maria Jasin & Rodney Rothstein, *Repair of Strand Breaks by Homologous Recombination*, 5 COLD SPRING HARBOR PERSP. BIOLOGY 1, 5 (2013).

35. Mattew H. Porteus & David Baltimore, *Chimeric Nucleases Stimulate Gene Targeting in Human Cells*, 300 SCI. 763, 763 (2003).

36. Matthew J. Moscou & Adam J. Bogdanove, *A Simple Cipher Governs DNA Recognition by TAL Effectors*, 326 SCIENCE 1501, 1501 (2009).

37. *See* Amy Maxmen, *The Genesis Engine*, WIRED (Aug. 2015) http://www.wired.com/2015/07/crispr-dna-editing-2/.

38. *Id.*

39. *Id.*

40. *See infra* Part III.

41. S. Antony Ceasar et. al., *Insert, Remove, or Replace: A Highly Advanced Genome Editing System Using CRISPR/Cas9,* 1863 BBA MOLECULAR CELL RES. 2333 (2016).

III. APPLICATIONS OF CRISPR

As with any newly developing technology, the advancement of the CRISPR system is still in its infancy. However, given the simplicity and the low cost of using CRISPR, researchers have already utilized CRISPR to create improved livestock and plants.[42] Targeted gene therapies for humans and animals will also likely be forthcoming.[43] The estimates of the economic impact of CRISPR are staggering for such a newly developed technology, with one estimate predicting a market of more than $5.54 billion by 2021.[44] This section will discuss a few of the recent CRISPR developments for humans, animals, and plants.

A. Human Applications of CRISPR

The current and potential applications of CRISPR to the human genome are amongst the most controversial. Many CRISPR supporters are keen to promote the potential of the system to cure genetic disorders.[45] The majority of CRISPR supporters believe that the power of the CRISPR system could potentially outpace the ability of policymakers to consider allowable applications and their related social implications.[46] Most moderate supporters argue that taking the time to evaluate the moral consequences of CRISPR will not necessarily be the death knell for the technology as a whole.[47] The extremist CRISPR supporters believe that "slowing down research has a massive human cost" and that CRISPR opponents should just "[g]et out of the way."[48]

Of course, CRISPR opponents are also prevalent and some even argue for a complete and total ban of the technology.[49] Commonly, these CRISPR

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42. *See* Heidi Ledford, *CRISPR, The Disruptor*, NATURE (June 3, 2015), http://www.nature.com/news/crispr-thedisruptor-1.17673.

43. *Id.*

44. *See Genome Editing/Genome Engineering Market Worth 5.54 Billion USD by 2021*, MARKETSANDMARKETS, http://www.marketsandmarkets.com/PressReleases/genome-editing-engineering.asp (last visited Aug. 28, 2017).

45. *See, e.g.*, Steven Pinker, Opinion, *The Moral Imperative for Bioethics*, BOS. GLOBE (Aug. 1, 2015), https://www.bostonglobe.com/opinion/2015/07/31/the-moral-imperative-for-bioethics/JmEkoyzlTAu9oQV76JrK9N/story.html.

46. *See* Edward Lanphier et al., *Don't Edit the Human Germ Line*, NATURE (Mar. 12, 2015), https://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111.

47. *See id.* at 411.

48. Pinker, *supra* note 45.

49. *See* Sarah Karlin, *Gene Editing: The Next Frontier in America's Abortion Wars*, POLITICO (Feb. 16, 2016), https://www.politico.com/story/2016/02/gene-editing-abortion-wars-219230.

opponents cite the potential for creation of "designer babies" and concern about the potential for grave social inequality.[50]

Nevertheless, the science of CRISPR has marched on even in light of the controversies, and human CRISPR applications currently in development are plentiful. Human diseases caused by genetic mutations are prime targets of CRISPR technology.[51] Scientists from China using CRISPR on nonviable fertilized embryos have already edited the gene responsible for β-thalassaemia, a potentially fatal blood disorder.[52] Other researchers using CRISPR have been able to permanently inactivate the human immunodeficiency virus (HIV) in human blood cells, representing a possible new avenue for curing AIDS in the human population.[53] Modification of the human genome could even potentially eradicate genetically inherited diseases like Down syndrome, cystic fibrosis, and Huntington's disease, as well as certain genetically linked cancers.[54]

In summary, the potential human applications of CRISPR are vast. In light of safety, morality, and regulatory concerns, only time will tell if these exciting applications will come to fruition.

B. Animal Applications of CRISPR

As CRISPR can be used to genetically edit virtually any germline cell, animals are also at the forefront of the technological applications. CRISPR has the potential to impact not only agriculturally important livestock animals, but also companion animals throughout the world.

Of course, CRISPR modification of animals can also be targeted to impact human health. For instance, researchers are exploring the possibility of altering the pig genome so that pigs could, in theory, grow human organs for transplant.[55] CRISPR can also repair defective DNA in mice and cure them of genetic disorders, which in turn could influence the cure of related human disorders.[56]

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50. *See id.*
51. *Id.*
52. *Id.*
53. *See* Rafal Kaminski et al., *Elimination of HIV-1 Genomes from Human T-Lymphoid Cells by CRISPR/Cas9 Gene Editing*, 6 SCI. REP. 1, 1–2 (Mar. 4, 2016), http://www.nature.com/articles/srep22555.
54. *See* David Cyranoski & Sara Reardon, *Chinese Scientists Genetically Modify Human Embryos: Rumors of Germline Modification Prove True -and Look to Reignite an Ethical Debate,* NATURE (April 22, 2015), http://www.nature.com/news/chinese-scientistsgenetically-modifyhuman-embryos-1.17378.
55. *See* Kristen V. Brown, *Inside the Garage Labs of DIY Gene Hackers*, *Whose Hobby May Terrify You*, FUSION (Mar. 29, 2016), http://projectearth.us/inside-the-garage-labs-of-diy-gene-hackers-whose-hobby-1796423884.
56. *See* Zimmer, *supra* note 23.

Other animals can benefit from the CRISPR platform, for example by instituting disease resistance into the genome. To combat the depletion of honeybees around the world due to disease and parasites, researcher Brian Gillis is investigating the genomes of "hygienic" honeybees for potential CRISPR application.[57] These hygienic bees are known to compulsively clean their hives in order to remove sick and infested bee larvae, and are shown to be less susceptible to mites, fungi, and other pathogens compared to other strains.[58] Identification of honeybee genomics associated with this hygienic behavior may lead to genomic editing via CRISPR to improve hive heath and to stem the worldwide honeybee depletion.

In addition, researchers at the University of Missouri have used CRISPR to modify cell surface proteins in pigs to make them virtually resistant to the deadly swine disease porcine reproductive and respiratory syndrome (PRRS).[59] According to estimates, PRRS costs producers in North America more than $600 million on an annual basis,[60] and there is no cure.[61] However, using CRISPR, the pig genome was edited to disable the protein responsible for entry of the virus into swine cells, and the modification actually resulted in protection from the deadly disease.[62]

CRISPR could also be used to make agriculture more humane. For example, long horns on cattle can cause injuries, so farmers generally remove the horns via burning, cutting, or chemical techniques.[63] Although polled cattle varieties exist, crossing these animals with more "elite" meat or dairy cattle breeds may reduce the quality of the resultant offspring.[64] CRISPR gene editing has been used to eliminate horns from cattle by transferring the non-horn gene from one species into an "elite" breed.[65]

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57. Sara Reardon, *Welcome to the CRISPR Zoo,* NATURE (Mar. 9, 2016), http://www.nature.com/news/welcome-to-the-crispr-zoo-1.19537.

58. *Id.*

59. Monique Brouillette, *You Can Edit a Pig, but it Will Still Be a Pig,* SCI. AM. (Mar. 2016) at A22, *subsequently published as,* Monique Brouillette, *Scientists Breed Pigs Resistant to a Devastating Infection Using CRIPSR*, SCI. AM. (Mar. 1, 2016), https://www.scientificamerican.com/article/scientists-breed-pigs-resistant-to-a-devastating-infection-using-crispr/.

60. *See* Derald J. Holtkamp et al., *Assessment of the Economic Impact of Porcine Reproductive and Respiratory Syndrome Virus on United States Pork Producers*, 21 J. OF SWINE HEALTH AND PROD. (2013).

61. *See Porcine Reproductive and Respiratory Syndrome (PRRS)*, PIG SITE, http://www.thepigsite.com/pighealth/article/142/porcine-reproductive-and-respiratory-syndrome-prrs/ (last visited Dec. 14, 2017).

62. Brouillette*, supra* note 59.

63. Reardon, *supra* note 57.

64. *Id*.

65. Wenfang Tan et al., *Efficient Nonmeiotic Allele Introgression in Livestock Using Custom Endonucleases*, 110 PROC. NAT'L. ACAD. SCI. U.S.16526–27 (2013).

Furthermore, CRISPR technology could result in a more fantastical application – reviving species of extinct animals.[66] Although talk of bringing back the wooly mammoth (*Mammuthus primigenius*) has existed for years, CRISPR may facilitate this undertaking by editing the genome of existing elephant species, such as the Indian elephant.[67] Such an application will require several more years of research, but could result in a Jurassic Park-like plotline becoming reality.

In summary, animal applications of CRISPR are far-reaching, but within the purview of researchers around the globe. Generally, given lower regulatory thresholds and fewer social morality issues, applications resulting from CRISPR editing of animal germlines may be more plentiful and faster to market than their human counterparts.

C. Plant Applications of CRISPR

Applications of CRISPR to the plant world have also flourished.[68] Published research demonstrates that plant modification via CRISPR is more successful, and also more efficient, than previously developed genetic engineering methods.[69] Importantly, thanks to CRISPR, curing crop diseases and creating crops that are immune to disease may soon become the normal course for genetically modified plants.[70]

The use of CRISPR for agriculturally important crops is of great significance given the rapidly growing global population. Although the global population has increased by approximately 60% over the past twenty years, grain production per capita has actually decreased worldwide.[71] If population growth rates continue according to the current pace, the world population will double again within fifty years, and estimates show that food production must also double by the year 2050 in order to keep up with demands.[72] Therefore, creating new ways to feed a growing population must be explored by any means necessary.

Several success stories of using CRISPR to modify crops have already emerged. For example, Chinese researchers using CRISPR developed a strain of wheat that is resistant to powdery mildew, a destructive fungal

66. Reardon, *supra* note 57.
67. *Id.*; *See also* Zimmer, *supra* note 23.
68. Doudna & Charpentier, *supra* note 28, at 1258096-5.
69. *Id.*
70. *See, e.g.*, Khaoula Belhaj et al., *Plant Genome Editing Made Easy: Targeted Mutagenesis in Model and Crop Plant Using The CRISPR/Cas System*, PLANT METHODS, (Oct. 11, 2013), at 1, https://plantmethods.biomedcentral.com/articles/10.1186/1746-4811-9-39.
71. Samir Suweis et al., *Resilience and Reactivity of Global Food Security*, 112 PROC. NAT'L. ACAD. SCI. U.S. 6902, 6902, 6905 (2015).
72. *Id.* at 6902.

pathogen.[73] The Chinese researchers edited the wheat genome to delete certain genes that encode proteins that repress defenses against the mildew.[74] Thus, simple genetic editing via CRISPR can stop mildew in its tracks, rather than using heavy doses of fungicides to control the disease.[75] The results are more effective and environmentally friendly compared to current methods.

Researchers have also successfully created tomatoes with prolonged life via CRISPR by turning off the genes that control how quickly the tomatoes ripen.[76] Furthermore, using CRISPR methods, researchers are working on engineering vegetables that possess enhanced nutrition.[77] Because vegetables can make their nutrients more available, such as lycopine and glucosinolates in broccoli, humans can benefit even more from eating their vegetables.[78]

There appears to be a myriad of CRISPR applications in the plant world, and agricultural companies are already on board.[79] For example, DuPont Pioneer has invested in Caribou Biosciences, the startup co-founded by CRISPR co-inventor Jennifer Doudna, which explores the use of genome editing on corn, soybeans, wheat, and rice.[80] DuPont Pioneer has announced plans to begin selling seeds made with CRISPR technology within five years.[81]

IV. INVENTORSHIP OF CRISPR

The CRISPR system's multitude of applications, both real and theoretical, is developing at a breakneck pace. But what was the first group to invest in CRISPR's function for gene editing? And, perhaps more importantly, which group owns the intellectual property rights to use CRISPR for gene editing? The final answer is yet to be determined, but is currently playing out in the U.S. Patent Office and perhaps in the federal court system.[82]

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73. David Talbot, *Chinese Researchers Stop Wheat Disease with Gene Editing*, MIT TECH. REV. (Jul. 21, 2014), https://www.technologyreview.com/s/529181/chinese-researchers-stop-wheat-disease-with-gene-editing/.

74. *Id.*

75. *Id.*

76. *See* Michael Specter, *The Gene Hackers*, NEW YORKER (Nov. 16, 2015), http://www.newyorker.com/magazine/2015/11/16/the-gene-hackers.

77. Jeannine Otto, *More Nutritious and Tastier Vegetables? CRISPR Gene Editing Could Dramatically Boost Consumption,* GENETIC LITERACY PROJECT (Feb. 16, 2017), https://www.geneticliteracyproject.org/2017/02/16/nutritious-tastier-vegetables-crispr-gene-editing-dramatically-boost-consumption/.

78. Specter, *supra* note 76.

79. Talbot, *supra* note 73.

80. *Id.*

81. Specter, *supra* note 76.

82. Otto, *supra* note 77.

The story of who invented the use of CRISPR for gene editing focuses on two research groups.[83] One research group was led by Dr. Jennifer Doudna at the University of California, Berkeley.[84] Dr. Doudna and French researcher, Emmanuelle Charpentier, were the first scientists to demonstrate that CRISPR could edit purified DNA, and published these findings in the journal *Science* in the summer of 2012.[85] The second research group was led by the laboratory of Dr. Feng Zhang of The Broad Institute of MIT and Harvard.[86] In early 2013, Dr. Zhang published research demonstrating that CRISPR could be used to modify human genes.[87]

The history of the patent applications arising from both Dr. Doudna's group and from Dr. Zhang's group is more complicated.[88] In March 2013, Dr. Doudna filed a patent application regarding the general CRISPR-Cas9 system, which included a whopping 155 claims.[89] In October 2013, Dr. Zhang filed a patent application and requested that the application be placed on the accelerated examination track by the United States Patent and Trademark Office (USPTO).[90]

Because of Dr. Zhang's request for his patent to be placed on the accelerated track, Dr. Zhang's patent was first issued on April 15, 2014.[91] Specifically, the patent granted Dr. Zhang the right to exclude others from implementing the commercial use of CRISPR technology for eukaryotic cells (e.g., cells of humans and other animals).[92] As a result, Dr. Zhang was granted control over CRISPR applications for use in humans, monkeys, pigs, and mice, which represent the majority of test models that can be used for advancement of human disease therapeutics.[93] In other words, with the grant of the patent, Dr. Zhang was given the keys to the vehicle that undoubtedly represents the possibility of generating the most profitable uses of CRISPR technology.

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83. Specter, *supra* note 76.
84. *Id.*
85. *Id.*
86. *Id.*
87. Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCI. 819, 822 (2013); *see also* Specter, *supra* note 76.
88. *See generally* Jacob S. Sherkow, *The CRISPR Patent Interference Showdown Is On: How Did We Get Here and What Comes Next*?, STAN L. SCH.: L. & BIOSCIENCES BLOG (Dec. 29, 2015), https://law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/.
89. U.S. Patent Application No. 13/842,859 (filed Mar. 15, 2013) (priority date May 25, 2012).
90. U.S. Patent No. 8,697,359 (filed Oct. 15, 2013) (issued Apr. 15, 2014).
91. Sherkow, *supra* note 88.
92. *Id.*
93. *Id.*

As filed, the two patent applications can seemingly be distinguished.[94] Dr. Doudna's patent application contained language that could be interpreted to limit the claims to apply CRISPR only to *prokaryotic* cells.[95] In contrast, Dr. Zhang's application claimed a method of performing CRISPR editing in *eukaryotic* cells.[96] In light of the patent grant to Dr. Zhang, Dr. Doudna's group amended the claims of their patent application to remove the suggestion that the claims are limited to prokaryotic cells.[97] This amendment provided Dr. Doudna the opportunity to request that the USPTO determine which competing party is truly entitled to a patent on CRISPR technology.[98]

Clearly, Dr. Doudna's patent application was filed first and thus was given an earlier priority date than Dr. Zhang's patent application. As a result, Dr. Doudna petitioned the USPTO to institute an interference proceeding in order to argue that Dr. Zhang's already issued patent "interfere[ed]" with Dr. Doudna's ability to obtain a patent on her earlier filed application.[99] The purpose of an interference proceeding is to determine which party was actually the first to invent a particular claimed technology.[100]

On January 11, 2016, the USPTO granted Dr. Doudna's request for an interference proceeding of the two patent filings, and a number of disputed claims between the two patent filings became at issue.[101] The interference proceeding was thereafter argued before a panel of judges in order to determine who was the true inventor. Several motions and oral proceedings were undertaken before the USPTO issued its decision.

During the interference proceeding, Dr. Zhang's group argued that the two competing patent filings actually represented different claims—Zhang's patent claiming CRISPR for use on eukaryotic cells, and Doudna's patent claiming CRISPR for use on prokaryotic cells like bacteria.[102] In contrast,

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94. *Id.*

95. '859 Patent Application ("The present disclosure provides genetically modified cells that produce Cas9; and Cas9 transgenic non-human multi-cellular organisms.").

96. '359 Patent.

97. Suggestion of Interference Pursuant to 37 C.F.R. § 41.202 at 7, In re Patent Application of Jennifer Doudna et al., U.S. Patent Application Serial No. 13/842,859 (Apr. 13, 2015).

98. *Id.* at 1.

99. *Id.*

100. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (codified as amended in scattered sections of 35 U.S.C.); Mark Summerfield, *CRISPR--Will This Be the Last Great US Patent Interference?*, PATENTOLOGY (July 11, 2015, 8:08 PM), http://blog.patentology.com.au/2015/07/crispr-will-this-be-last-great-us.html.

101. Declaration – 37 C.F.R. § 41.203(b) at 2, Broad Inst. Inc. v. Regents of the Univ. of Cal., No. 106,048 (P.T.A.B. Jan. 11, 2016); Heidi Ledford, *Bitter Fight Over CRISPR Patent Heats Up*, NATURE (Jan. 12, 2016), http://www.nature.com/news/bitter-fightover-crispr-patent-heats-up-1.17961.

102. Heidi Ledford, *Broad Institute Wins Bitter Battle Over CRISPR Patents*, NATURE (Feb. 15, 2017), http://www.nature.com/news/broad-institute-wins-bitter-battle-over-crispr-patents-1.21502.

Dr. Doudna's group argued that their patent filing dominated the later patent filing by Dr. Zhang because Dr. Doudna's patent application covered all aspects of CRISPR, not just prokaryotes.[103] In other words, Dr. Doudna asserted that her group was the rightful owner of the patent issued to Dr. Zhang because they, in fact, invented the technology first.

In a decision rendered in February 2017, the USPTO upheld the patents issued to Dr. Zhang's group, stating that the patents were valid because they were distinguishable from the patent filings of Dr. Doudna's group.[104] As a result, the USPTO found that the most lucrative applications of CRISPR technology, the editing of eukaryotic cells such as humans, animals, and plants, belong to Dr. Zhang and The Broad Institute.[105] The decision was immediately reflected in the business world, as stock in Editas Medicine, a biotechnology company that licensed the CRISPR patents owned by The Broad Institute, surged following announcement of the USPTO verdict.[106]

However, the battle over CRISPR patent rights is far from over. Dr. Doudna's group could appeal the USPTO's decision and further challenge the ownership of the patents. Alternatively, there is still the possibility for the two competing groups to reach a settlement agreement. Moreover, the patent rights outside the United States are still up for grabs and a patent battle may be forthcoming in other jurisdictions, such as Europe.[107]

In the wake of the USPTO's decision, both Dr. Doudna and Dr. Zhang were allowed to maintain ownership of their respective patents.[108] However, the USPTO interim decision has created a cloud of uncertainty for entities that desire to use CRISPR gene editing in eukaryotic cells. For example, it is unclear if a license for using CRISPR on eukaryotic cells must be obtained from the University of California, Berkeley (the owner of the Doudna patents), The Broad Institute (the owner of the Zhang patents), or both.[109] If researchers are compelled to obtain a license from both entities, the cost of commercializing CRISPR technology may ultimately increase.[110] However, it does not appear that the ongoing patent rights battle has slowed down research on utilizing CRISPR; in fact, many groups have developed new

103. *Id.*
104. *Id.*
105. *Id.*
106. *Id.*
107. Heidi Ledford, *Why the CRISPR Patent Verdict Isn't the End of the Story*, NATURE (Feb. 17, 2017), http://www.nature.com/news/why-the-crispr-patent-verdict-isn-t-the-end-of-the-story-1.21510.
108. *Id.*
109. *Id.*
110. Jon Cohen, *How the Battle Lines Over CRISPR Were Drawn,* SCIENCE (Feb. 15, 2017), http://www.sciencemag.org/news/2017/02/how-battle-lines-over-crispr-were-drawn.

methods that may be outside the scope of the claims of *both* the Doudna and Zhang patents.[111]

In summary, The Broad Institute won an important early victory in the battle for ownership of CRISPR applications. However, the jury is still out on who will be the ultimate victor in the war. In the meantime, the science surrounding CRISPR continues to march on by exploring even more innovative pathways.

V. REGULATORY ASPECTS OF CRISPR-EDITED PRODUCTS

As discussed previously, the phrase "genetically modified organism" evokes strong feelings and beliefs from both proponents and opponents of GMOs.[112] However, the unique mechanism of the CRISPR system presents an opportunity to redefine how "gene edited" animals and plants are viewed by scientists, regulators, and consumers. Before exploring CRISPR's varied regulatory aspects in human, animal, and plant organisms, it is informative to understand the scope of how "traditionally viewed" GMOs are regulated.

A. Current Regulation of GMOs

Generally, there are two processes by which GMOs are regulated by worldwide agencies. The first view is a *product-focused* approach that evaluates the final genetically modified product compared to the natural, unmodified product.[113] Alternatively, the second view is a *process-focused* approach that emphasizes review of the actual process by which the GMO is produced.[114] The biotechnology industry prefers regulation that is product-focused because the genetic modification process itself is not stigmatized during evaluation of a GMO. However, in the end, both product *and* process focused regulatory reviews consider the method that is used to produce the GMO, although method of production is considered less in the product-focused review.[115]

In the United States, there is no federal legislation specifically directed to review GMOs.[116] Instead, GMOs are regulated by various existing government agencies that are set up to evaluate the health, safety, and environmental impact of the products under the Coordinated Framework for Regu-

111. *Id.*
112. *See infra* Part I.
113. S.J. Mayer, *The Regulation of Genetically Modified Food*, *in* 13 BIOTECHNOLOGY 91 (Horst Werner Doelle et al., eds., 2009).
114. *Id.*
115. *Id.*
116. *Restrictions on Genetically Modified Organisms: United States*, LIBR. OF CONGRESS (Jun. 9, 2015), https://www.loc.gov/law/help/restrictions-on-gmos/usa.php.

lation of Biotechnology, published in 1986.[117] According to this regulation, there are three tenets: "(1) U.S. policy would focus on the product of genetic modification (GM) techniques, not the process itself, (2) only regulation grounded in verifiable scientific risks would be tolerated, and (3) GM products are on a continuum with existing products and, therefore, existing statutes are sufficient to review the products."[118]

The process of regulatory review and approval varies depending on the type of GMO.[119] For example, "food, drug, and biological product GMOs are regulated under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act . . . by the Food and Drug Administration (FDA)."[120] Plant GMOs are regulated according to the "Animal and Plant Health Inspection Service by the U.S. Department of Agriculture (USDA) under the Plant Protection Act."[121] Pesticide and microorganism GMOs are regulated pursuant to the "Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act by the Environmental Protection Agency (EPA)."[122]

Compared to other countries, regulation on GMO development in the United States is relatively favorable.[123] For the U.S., GMOs are very important to the biotechnology industry from an economic standpoint.[124] For example, the U.S. leads the world in producing genetically modified crops.[125] In 2012, there were 420.8 acres of biotech crops worldwide, and the U.S. accounted for over 40% of this production (171.7 acres).[126] Furthermore, the majority of several different types of crops grown in the U.S. are now comprised of genetically engineered varieties.[127] For instance, in 2013, 93% of the soybeans, 90% of the cotton, and 90% of the corn grown in the U.S. were genetically engineered crops, due to either herbicide tolerance or an insect resistance.[128]

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117. *Id.*

118. Emily Marden, *Risk and Regulation: U.S. Regulatory Policy on Genetically Modified Food and Agriculture*, 44 B.C. L. REV. 733, 738 (2003).

119. LIBR. OF CONGRESS, *supra* note 116.

120. *Id.*

121. *Id.*

122. *Id.*

123. *Restrictions on Genetically Modified Organisms: United States,* LIBR. OF CONGRESS, https://www.loc.gov/law/help/restrictions-on-gmos/usa.php#skip_menu (last updated Jun. 09, 2015).

124. *Id.*

125. *Id.*

126. CLIVE JAMES, INT'L SERV. FOR THE ACQUISITION OF AGRI-BIOTECH APPLICATIONS, BRIEF 44: GLOBAL STATUS OF COMMERCIALIZED BIOTECH/GM CROPS 7 (2012).

127. *See Recent Trends in GE Adoption*, U.S. DEP'T OF AGRIC., ECON. RES. SERV., http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-ge-adoption.aspx#.UobvBXL92Dk (last updated July 12, 2017).

128. *Id.*

On the other side of the spectrum, the regulation of GMOs in the European Union (EU) is vastly different. Regulatory laws passed in 2003 caused the EU to have possibly the most stringent GMO regulations in the world, which primarily utilize the process-based approach to regulatory review.[129]

As of 2010, the EU considers all GMO crops to be "new foods."[130] As a result, each GMO crop is subjected to an extensive, scientific-based evaluation by the European Food Safety Authority (EFSA) on a case-by-case basis.[131] In turn, the EFSA agency reports to the European Commission (EC), which proceeds to draft proposals to either grant or refuse authorization of the GMO crop for submission to the "Section on GM Food and Feed of the Standing Committee on the Food Chain and Animal Health."[132] If accepted, the proposal is then either adopted by the European Commission or is passed on to the Council of Agricultural Ministers.[133] Thereafter, the Council has a three-month window to either vote for or against the proposal, and if a majority vote is not achieved, the proposal returns to the EC, which then adopts it.[134] The extreme amount of regulatory review and oversight over GMO crops, divided between multiple agencies within the EU, can result in tremendous delays in garnering approval.

The role of the EFSA is to use independent scientific research to advise the EU in order to protect not only consumers but also the environment.[135] This risk assessment includes evaluations to the molecular characterization of the GMO crop, its potential toxicity, and also its potential to impact the environment.[136] Each GMO that is approved must be reassessed every 10 years.[137] Moreover, applicants desiring to cultivate or to process the GMOs must further deliver a detailed surveillance plan outlining the steps to be taken after GMO authorization.[138] In other words, even after garnering an approval in the EU, the GMO crop is still subject to multiple layers of regulatory review.

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129. John Davison, *GM plants: Science, Politics and EC regulations*, 178 PLANT SCI. 94, 94 (2010).

130. *Id.*

131. *Id.* at 95.

132. *Id.*

133. *Id.*

134. *Id.*

135. EFSA, http://www.efsa.europa.eu/ (last visited Mar. 4, 2017).

136. *Genetically Modified Organisms,* EFSA, https://www.efsa.europa.eu/en/topics/topic/genetically-modified-organisms (last visited Mar. 4, 2017).

137. *Id.*

138. *Monitoring Plans and Reports*, EFSA, http://ec.europa.eu/food/plant/gmo/post_authorisation/plans_reports_opinions_en (last visited Mar. 4, 2017).

B. Regulation of CRISPR Human Applications

In the United States, the FDA has the responsibility to review all gene transfer therapy products and research for both safety and effectiveness.[139] In this context, the term "gene-therapy products" refers to biologically based articles, such as articles that are removed from a human patient, modified outside the body, and then placed back into the human patient.[140] Furthermore, "gene-therapy products" also include both natural and synthetic articles that are introduced to a human patient in order to genetically alter the patient's cells.[141]

Research protocols that are reviewable by the FDA comprise transmissions of genetic material into a human patient for the purpose of replacing absent or defective DNA in an attempt to treat or cure a disease in the patient.[142] Such a protocol is defined as a clinical trial, which would necessitate approval by the FDA.[143]

However, even in light of the broad authority of the FDA to regulate gene-therapies and research protocols, the FDA's regulation of the use of the CRISPR system to actually modify the human genome is uncertain.[144] As pure genetic material and embryos are not technically "human subjects," the FDA technically does not have the authority to regulate products and research protocols related to human germline modification.[145] In other words, scientists may perform experiments on human embryos and genetic material as long as the items are not "aimed at the development of a 'product' subject to its approval."[146]

Once a CRISPR-edited organism begins to be developed as a product or is the subject of development requiring clinical trials, the regulatory review of these activities would fall squarely within the FDA's purview. Thus, gene therapies utilizing the CRISPR system with the intention of treating human patients are subject to the stringent review procedures that other drugs and biologics must currently follow in order to garner FDA approval.

History has shown that as the FDA becomes more comfortable with a particular system of therapeutics, the path to approval is somewhat standardized as later registered products can build off of the successes of previously

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139. *Modification of Traits and Characteristics*, *in* REPRODUCTION AND RESPONSIBILITY: THE REGULATION OF NEW BIOTECHNOLOGIES 105, 110–11 (2004) [hereinafter REPRODUCTION AND RESPONSIBILITY].

140. *Id.* at 111.

141. *Id.*

142. *Id.*

143. *Id.*

144. PAUL KNOEPFLER, GMO SAPIENS: THE LIFE-CHANGING SCIENCE OF DESIGNER BABIES 258 (2015).

145. REPRODUCTION AND RESPONSIBILITY, *supra* note 139, at 111.

146. *Id.* at 131.

accepted products. However, as the early human applications of CRISPR editing are currently blazing new trails within the FDA, the agency will undoubtedly maintain a watchful eye on these therapies in the near future.

C. Regulation of CRISPR Animal Applications

Like human applications of CRISPR, the use of gene editing on animals intended for food would be governed in the United States by the FDA.[147] This process appears to be relatively straightforward, given that the FDA currently regulates genetically engineered animals.

On January 18, 2017, two days before President Obama left office, the FDA released three proposed regulations addressing different categories of products.[148] In particular, one proposal was directed to regulation of "intentionally altered" DNA in animals.[149] According to this draft proposal, the review of *all* animals with an "intentionally altered" genome would be subject to evaluation for safety and efficacy in a manner similar to the review process for new drugs.[150]

This proposed regulation was immediately met with criticism from CRISPR researchers. Given the accuracy and precision of the CRIPSR process to edit an animal's genome without the introduction of nonnative DNA, researchers were hopeful that these gene-editing products would be regulated less stringently than animals that are genetically engineered by introducing foreign DNA.[151] Furthermore, the inclusion of an "'intent"' element in the proposed regulation was also questioned.[152] Because the U.S. has generally followed a product-based approach to regulating genetically-altered animals, many researchers were baffled as to why animals with an "intentionally altered" genome would be subjected to increased scrutiny.[153] "The trigger for their regulation is whether the animal was intended to be made, and what does intention have to do with risk," commented Alison van Eenennaam, an animal geneticist at the University of California, Davis. "The risk has to do with the attributes of the product."[154]

147. Amy Maxmen, *Gene-Edited Animals Face US Regulatory Crackdown,* NATURE (Jan. 19, 2017), http://www.nature.com/news/gene-edited-animals-face-us-regulatory-crackdown-1.21331.

148. *Id.*

149. *Guidance for Industry – Regulation of Intentionally Altered Genomic DNA in Animals*, FDA (Jan. 2017), https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf.

150. *Id.*

151. Maxmen, *supra* note 147.

152. *Id.*

153. *Id.*

154. *Id.*

In particular, many people are concerned that, if implemented, the proposed regulations would result in the development of CRISPR-edited animals to slow down or to be abandoned completely by researchers.[155] In other words, the increased regulation of the animals via FDA review may cause businesses and universities to think twice before investing the time and effort to create improved animals via gene editing. Those who cannot remember the past are condemned to repeat it, and such companies undoubtedly recall the development of genetically engineered salmon by AquaBounty Technologies.[156]

In 1995, AquaBounty began the approval process for the development of an Atlantic salmon (*Salmo salar*) engineered with genes from Chinook salmon (*Oncorhynchus tshawytscha*) in order to promote rapid growth of the genetically modified fish.[157] However, the path to regulatory approval was lengthy and laborious. AquaBounty had to perform over 50 studies to demonstrate that the genetically modified salmon posed no unusual risks before the FDA finally approved the fish for sale in November 2015.[158] In total, AquaBounty spent approximately $60 million on the development of the fish. Even after gaining approval, the FDA later determined that the salmon cannot be sold in the United States until a final determination is made on whether the fish must be labeled as genetically modified.[159]

The FDA's proposed regulation in January 2017 was a setback to scientists currently engaged in the development of CRISPR-edited animals. For example, the gene editing company Recombinetics, located in St Paul, Minnesota, has developed hornless dairy cattle by using gene editing.[160] The gene editing to create the polled animal inserts a gene from naturally hornless beef cattle into a breed of the same species used in milk production.[161] As discussed previously, this process could ease animal welfare concerns associated with the removal of horns via burning, cutting, or chemical techniques.[162]

In December 2016, Recombinetics informed the FDA that it intended to sell food from the genetically edited cattle without receiving FDA approval, which is allowable if the food label states that the product is "generally recognized as safe."[163] However, with the uncertainty surrounding the

155. *Id.*
156. *Id.*
157. Amy Maxmen, *Transgenic Fish Wins US Regulatory Backing*, NATURE (Dec. 22, 2012), http://www.nature.com/news/transgenic-fish-wins-us-regulatory-backing-1.12130.
158. Maxmen, *supra* note 147.
159. *Id.*
160. *Id.*
161. *Gene-editing Options,* CATTLE BUSINESS WEEKLY (Jan. 25. 2017), http://cbw60.1upprelaunch.com/Content/Headlines/-Headlines/Article/Gene-editing-options/1/1/8660.
162. *See supra* Part III B.
163. Maxmen, *supra* note 147.

newly proposed FDA regulation, this decision has been thrown into jeopardy.

It is important to note that the January 2017 documents published by the FDA are simply proposals, and full implementation of the proposed procedures will take time, if they happen at all. The draft regulations are subject to receive public comments until April 2017; based on feedback, the regulatory approach may be further modified by the FDA.[164] Moreover, it is uncertain how the new administration under President Trump will oversee the proposed regulations. In the end, the proposed regulations have been the subject of many discussions for the future of CRISPR's animal editing, and it remains to be seen whether they represent a speed bump or a roadblock for future developments.

D. Regulation of CRISPR Plant Applications

In the U.S., plants with genetic modifications or genetic editing are regulated by the USDA.[165] In contrast to human and animal applications of CRISPR, the regulatory pathway for CRISPR-edited plants has already been assessed, both in the United States and abroad.

In April 2016, the USDA determined that a CRISPR-edited mushroom developed by scientists at Penn State University did not have to undergo regulation in the United States prior to being placed on sale.[166] Dr. Yinong Yang, the plant pathologist credited with the creation, used CRISPR to edit the common white button mushroom (*Agaricus bisporus*) so that it would resist browning.[167] By editing the mushroom to knock out one gene from the enzyme family that leads to browning, Dr. Yang successfully reduced the enzyme's activity by 30%.[168] In its evaluation, the USDA determined that since the edited mushroom did not contain any foreign genetic material, and did not represent "a plant pest or weed," regulation by the agency was unnecessary.[169]

Furthermore, the USDA has also determined that other gene-edited plants (including corn, potatoes, and soybeans that have been edited using

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164. *Id.*

165. Erin Brodwin, *Everything You Think You Know About Genetically Modified Food Is About to Change,* BUS. INSIDER (Apr. 14, 2016), http://www.businessinsider.com/the-us-government-says-crop-edited-with-crispr-wont-be-regulated-2016-4.

166. Emily Waltz, *Gene-edited CRISPR Mushroom Escapes US Regulation,* NATURE (Apr. 14. 2016), http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754.

167. *Id.*

168. *Id.*

169. Julienne Isaacs, *CRISPR-Cas9: A Promising Tool for Plant Breeding*, TOP CROP MANAGER (Oct. 3. 2016), http://www.topcropmanager.com/plant-breeding/crispr-cas9-a-promising-tool-for-plant-breeding-19611.

TALENs instead of CRIPSR) do not require evaluation, according to existing regulations.[170] This decision offers hope to companies and researchers pursuing gene-edited crops using CRISPR technology. However, the current regulations are under review and may change in the future.

The review of CRISPR applications to plants is also being conducted abroad. Similar to the United States, countries such as Argentina have indicated that genetically edited plants using CRISPR or TALENs are outside of the scope of existing GMO legislation.[171] In Canada, products are evaluated according to the new "trait" introduced in the plant instead of the process by which the plant was developed.[172] Moreover, the Canadian Food Inspection Agency (CFIA) must assess the environmental safety profile of plants comprising novel traits before the associated product can be released.[173] The jury is still out in China, where authorities have not yet decided whether CRISPR-edited crops will be able to be planted.[174]

But the biggest domino yet to fall is if the EU will ultimately decide to regulate CRISPR-edited plants. As discussed previously, the EU has some of the strictest regulations in the world with respect to GMO crops. However, given the differences in CRISPR technology with older methods for genetically modifying plants, the EU may follow the lead of the USDA and determine that CRISPR editing falls outside of the scope of current GMO regulations.

A promising development for proponents of CRISPR in the EU came in late 2015, when the Swedish Board of Agriculture determined that some plants edited using CRISPR technology did not fall under the rigorous EU definition of a GMO.[175] The Board issued its decision following an inquiry from researchers in Umeå and Uppsala in Sweden, and rendered an opinion that although some Arabidopsis plants modified using CRISPR fall within the scope of the EU's GMO definition, other plants do not.[176]

Following the decision in Sweden, the EU has not issued a definitive ruling regarding CRISPR editing in plants. Although the battle is far from over, the opening salvo by at least one country's board of agriculture has offered hope for scientists and researchers that plant improvements achieved

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170. Talbot, *supra* note 73.

171. *"Green Light in the Tunnel"! Swedish Board of Agriculture: a CRISPR-Cas9-mutant but Not a GMO*, UMEÅ PLANT SCI. CENTRE (Dec. 19, 2016), https://www.upsc.se/about-upsc/news/4815-green-light-in-the-tunnel-swedish-board-of-agriculture-a-crispr-cas9-mutant-but-not-a-gmo.html.

172. Isaacs, *supra* note 169.

173. *Id.*

174. Talbot, *supra* note 73.

175. *CRISPR-Cas9-edited Plant Genomes May Not Be Classified as GMOs*, PHYS. ORG. (Nov. 17, 2015), https://phys.org/news/2015-11-crispr-cas9-edited-genomes-gmos.html.

176. *Id.*

by CRISPR may be easier to bring to market in Europe than their GMO counterparts.

E. Recommendations on Future Regulation of CRISPR-Edited Products

As technological advancement continues to carry on, the regulation of new scientific breakthroughs in the medical and agricultural industries is an important consideration. Although regulators and policy makers may be tempted to simply try and include CRISPR and other gene editing platforms into the existing framework of GMO regulations, the opinion of this author is that the CRISPR revolution provides a unique opportunity to redefine regulation of such groundbreaking products.

Regardless of whether current GMO regulations are *product* or *process* focused, the same concerns underlie the regulatory context. For instance, the safety and efficacy of the genetically modified product must be considered, both for the organism being modified and for the consumer that will utilize the product. In addition, environmental concerns must also be addressed to ensure that the natural world will not be untowardly affected by the genetic modification. Regulatory review of a GMO product is a complex undertaking that must balance the interest of the public, the affected organism, and the environment.

However, the difficulty in performing this balancing act is considerably lessened when considering an organism that undergoes gene editing with CRISPR. The CRISPR system is simple and inexpensive for researchers to utilize.[177] Furthermore, CRISPR modifications have the potential to improve the health and well-being of the consumer.[178] In the human and the animal fields, genetic editing via CRISPR is being developed to treat and even cure diseases.[179] In addition, in the field of agricultural biotechnology, modification of livestock and crops using CRISPR is one possible solution to address the problem of feeding an ever-increasing world population.[180]

Perhaps most importantly, the negative stigma sometimes associated with genetically modified organisms may be eased if an explanation of the genetic editing process is properly communicated to the general public. Many people's perception of GMOs can be summarized in one term: "Frankenfish."[181] Critics view genetically modified organisms as a grotesque laboratory creation that represent an unnatural cobbling together of unrelated organisms to create a monstrous mutant, even when such GMOs have

177. *See* Ledford, *supra* note 42 and accompanying text.
178. *See supra* Part III A.
179. *Id*.
180. *Supra* Part III C.
181. *'Frankenfish' Salmon Won't Be Labeled: FDA*, NEW YORK POST (Nov. 20, 2015), http://nypost.com/2015/11/20/frankenfish-salmon-coming-soon-to-a-supermarket-near-you/.

undergone years of careful regulatory review and approval. This perception is difficult for many detractors to overcome, especially when the genome of one particular organism is in fact modified using genetic material from a second organism.

However, gene editing using CRISPR alleviates these concerns. The CRISPR system does not insert nonnative genes into an organism's genome – it simply corrects that organism's defective or non-functioning gene and restores it to a proper, functioning state. In other words, following the CRISPR system, the end product is comprised solely of its own genetic material.[182] Thus, the impression of an outrageous "Frankenfish" being thrust upon the public should be eliminated if the public fully understands CRISPR's precise and targeted gene editing techniques.

In crafting new regulations for CRISPR-edited organisms, policy makers should pay careful attention to the fact that the gene editing procedure simply corrects defective genetic material in an organism, or replaces the defective genetic material with functioning genes from the organism's own genome. The end product is typically indistinguishable from naturally occurring organisms that have not undergone a gene editing process. Moreover, CRISPR can improve not only the end user but also the welfare of the edited organism itself, as observed by the previously described animal applications.[183]

The FDA and USDA, as well as corresponding regulatory agencies worldwide, can learn from their previous experiences in regulating GMOs to guide regulation of CRISPR technology. First, with the rapid speed that CRISPR is developing, the agencies should announce a framework for review sooner rather than later. Second, the agencies should ensure that they gather information from all interested parties in crafting new rules for regulation. Concerns from both CRISPR advocates and CRISPR opponents should be expressed and considered in the rulemaking process. Finally, the agencies should articulate clear standards for the regulatory approach, including a comparison of the CRISPR process with previously used genetic modification procedures. Given the benefits in using CRISPR gene editing compared to older methods, it would be beneficial if agencies address the regulations in the context of scientific progress instead of simply maintaining the status quo for a possibly outdated GMO approval process.

VI. CONCLUSION

CRISPR technology is moving at a breakneck pace. Although regulatory concerns are certainly valid, the benefits offered by the new technology

182. *See supra* text accompanying note 7.
183. *See supra* Part III B.

are also significant for the medical and agricultural world. Thus, it will be imperative for researchers and regulators to find common ground so that these valuable innovations can be brought to market for the benefit of mankind.