GENE EDITING: BIOTECHNOLOGY BREAKTHROUGHS AND CHALLENGES

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CRISPR, an acronym for Clustered Regularly Interspaced Short Palindromic Repeats, is a novel gene editing technology that has been called one of the greatest scientific discoveries in the last century.[1] 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.[2] This amazing process results in an organism with a corrected genetic sequence. In some cases, the organism with corrected genetic sequence is made up entirely of its own native genes and is indistinguishable from an organism that has undergone natural breeding selection.[3]

The instances in which 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.[4] 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.[5] 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.[6]

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.[7]

In summary, CRISPR is a game changer for defining what is and what is not a genetically modified organism. This paper will explain the science of using the CRISPR system as a genetic editing

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[1] *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/.
[2] *Id*.
[3] *Id.*
[4] *Id.*
[5] *Id.*
[6] https://www.sciencedaily.com/releases/2015/10/151019123744.htm
[7] 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/.

tool,[8] the current and potential applications of CRISPR in animals and plants,[9] the important battle over the inventorship of the CRISPR process that will ultimately determine the true owner of the technology,[10] and the growing regulatory quandary faced by various countries on how to classify organisms modified by CRISPR.[11]

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.[12] 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).[13] 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.[14] CRISPR is represented by short DNA sequences followed by the same DNA sequence in reverse, also known as the "palindromic sequence."[15] 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.[16] These DNA sequences represent a significant portion of the bacterial genome and almost all archaea, a domain and kingdom of single-celled microorganisms.[17] For many years, the scientific community assumed that these sequences were nothing more than "junk" DNA due to the frequency of seemingly unimportant repetition in the sequences.[18] This assumption, however, fell by the wayside as more and more genomic information became available to scientists in the 1990s and 2000s.[19]

In 2005, researchers discovered that the spacer DNA sequences in the bacterial genome actually matched the DNA sequences known to be present in viruses.[20] This breakthrough indicated that that the spacer DNA sequences may not be junk DNA after all and ultimately suggested a role in microbial immunity.[21] 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.[22] 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.

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[8] See *infra* Part II.
[9] *See infra* Part III.
[10] *See infra* Part IV.
[11] *See infra* Part V.
[12] *See, e.g.*, Asude Alpman Durmaz et al., *Evolution of Genetic Techniques: Past, Present, and Beyond*, BIOMED RES. INT'L 1, 1 (2014).
[13] https://ghr.nlm.nih.gov/primer/basics/dna
[14] 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).
[15] Elizabeth E. Pennisi, *The CRISPR Craze*, 341 SCI. 833, 834 (2013).
[16] Stern et al., *supra* note 18, at 1015.
[17] *Id.*
[18] *Id.* (due to the repetitive nature of REP sequences, it was assumed that DNA only reflected nonsense "junk" sequences in the genome).
[19] *See* Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG., Feb. 6, 2015, https://www.quantamagazine.org/20150206-CRISPR-dna-editor-bacteria.
[20] *Id.*
[21] *Id.*
[22] *Id.*

Dr. Jennifer A. Doudna, a researcher at the University of California, Berkeley, discovered how bacteria utilize CRISPR spacer DNA (crDNA) as a defense mechanism.[23] 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.[24] Cas9 is an enzyme that cuts the identified viral DNA at the end of the crRNA complementary sequence, thus inactivating the virus.[25] 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.[26] 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 protein to cut DNA at a specific point.[27] The innovative aspect of the CRISPR-Cas9 system is that it uses a RNA-based recognition of DNA instead of a protein-based recognition.[28] 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.[29]

Scientists developed several competing genetic-editing technologies before CRISPR, including meganucleases,[30] zinc finger nucleases (ZFNs),[31] and transcription activator-like effector nucleases (TALENs).[32] 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.[33] 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.[34] 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.[35] The CRISPR system then incorporates a corrected sequence into the genome provided by scientists to "fix" the cut DNA sequence.

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[23] *See* Dipali G. Sashital et al., *Mechanism of Foreign DNA Selection in a Bacterial Adaptive Immune System*, 46 MOLECULAR CELL 606, 606 (2012).
[24] 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).
[25] *Id*. at 1258096-2.
[26] *Id*. at 1258096-1to -5.
[27] Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCI. 816, 819–20 (2012).
[28] *Id.*
[29] Pennisi, *supra* note 19, at 835.
[30] Maria Jasin & Rodney Rothstein, *Repair of Strand Breaks by Homologous Recombination*, 5 COLD SPRING HARBOR PERSP. BIOLOGY 1, 5 (2013).
[31] Mattew H. Porteus & David Baltimore, *Chimeric Nucleases Stimulate Gene Targeting in Human Cells*, 300 SCI. 763, 763 (2003).
[32] Matthew J. Moscou & Adam J. Bogdanove, *A Simple Cipher Governs DNA Recognition by TAL Effectors*, 326 SCI. 1501, 1501 (2009).
[33] *See* Amy Maxmen, *The Genesis Engine*, WIRED, Aug. 2015, http://www.wired.com/2015/07/crispr-dna-editing-2/.
[34] *Id.*
[35] *Id.*

However, in 2018, research demonstrated that changes in DNA can be introduced by CRISPR edits at a farther distance from the target location to be edited than was previously known.[36] Further, in a somewhat concerning revelation, standard DNA tests may not normally detect this damage. Previous identification of damage from CRISPR-induced edits was conducted relatively close to the original edit and did not generally find any signs of harm. The research determined that in some cases, the newly identified changes introduced fairly large deletions or insertions, possibly leading to DNA being either switched on or off at inappropriate times as a result of the edits. Although these new findings do not necessarily invalidate the CRISPR approach to gene editing, they certainly represent a good reason for scientists to pay attention to their data in order to address the concerns.

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.[37] Genetic modifications using CRISPR can be used to activate, add, delete, or suppress genes. 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.

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.[38] Targeted gene therapies for humans and animals will also likely be forthcoming.[39] 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.[40] This section will discuss a few of the recent CRISPR developments for animals and plants.

A. 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.[41] 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.[42]

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

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[36] https://www.extremetech.com/extreme/274110-study-suggests-crispr-gene-editing-could-have-unanticipated-side-effects

[37] *See infra* Part III.

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

[39] *Id.*

[40] *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).

[41] *See* Kristen V. Brown, *Inside the Garage Labs of DIY Gene Hackers*, *Whose Hobby May Terrify You*, FUSION (Mar. 29, 2016, 7:00 AM), http://projectearth.us/inside-the-garage-labs-of-diy-gene-hackers-whose-hobby-1796423884.

[42] *See* Zimmer, *supra* note 23.

CRISPR application.[43] 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.[44] 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).[45] According to estimates, PRRS costs producers in North America more than $600 million on an annual basis,[46] and there is no cure.[47] 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.[48]

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.[49] Although polled cattle varieties exist, crossing these animals with more "elite" meat or dairy cattle breeds may reduce the quality of the resultant offspring.[50] CRISPR gene editing has been used to eliminate horns from cattle by transferring the non-horn gene from one species into an "elite" breed.[51]

Furthermore, CRISPR technology could result in a more fantastical application – reviving species of extinct animals.[52] 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.[53] 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.

B. Plant Applications of CRISPR

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[43] Sara Reardon, *Welcome to the CRISPR Zoo,* NATURE (Mar. 9, 2016), http://www.nature.com/news/welcome-to-the-crispr-zoo-1.19537.
[44] *Id.*
[45] 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/.
[46] *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).
[47] *See Porcine Reproductive and Respiratory Syndrome (PRRS)*, THE PIG SITE, http://www.thepigsite.com/pighealth/article/142/porcine-reproductive-and-respiratory-syndrome-prrs/ (last visited Dec. 14, 2017).
[48] Brouillette*, supra* note 59.
[49] Reardon, *supra* note 57.
[50] *Id*.
[51] Wenfang Tan et al., *Efficient Nonmeiotic Allele Introgression in Livestock Using Custom Endonucleases*, 110 PROC. NAT'L. ACAD. SCI. U.S.16526–27 (2013).
[52] Reardon, *supra* note 57.
[53] *Id*.; *See also* Zimmer, *supra* note 23.

Applications of CRISPR to the plant world have also flourished.[54] Published research demonstrates that plant modification via CRISPR is more successful, and also more efficient, than previously developed genetic engineering methods.[55] 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.[56]

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.[57] 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.[58] 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 pathogen.[59] The Chinese researchers edited the wheat genome to delete certain genes that encode proteins that repress defenses against the mildew.[60] Thus, simple genetic editing via CRISPR can stop mildew in its tracks, rather than using heavy doses of fungicides to control the disease.[61] 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.[62] Furthermore, using CRISPR methods, researchers are working on engineering vegetables that possess enhanced nutrition.[63] Because vegetables can make their nutrients more available, such as lycopine and glucosinolates in broccoli, humans can benefit even more from eating their vegetables.[64]

In June 2018, Dr. Michael Gomez, working with partners at the Innovative Genomics Institute, announced that he had succeeded in removing genes from cassava (known in North America as the tapioca product). Cassava is an important crop in Africa and many countries in the southern hemisphere due to its drought resistant properties. Removal of the genes that are responsible for excessive cyanide production in cassava could result in a huge increase in the usefulness of the crop as a food source in these regions.

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[54] Doudna & Charpentier, *supra* note 28, at 1258096-5.
[55] *Id.*
[56] *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.
[57] Samir Suweis et al., *Resilience and Reactivity of Global Food Security*, 112 PROC. NAT'L. ACAD. SCI. U.S. 6902, 6902, 6905 (2015).
[58] *Id.* at 6902.
[59] 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/.
[60] *Id.*
[61] *Id.*
[62] *See* Michael Specter, *The Gene Hackers*, THE NEW YORKER (Nov. 16, 2015), http://www.newyorker.com/magazine/2015/11/16/the-gene-hackers.
[63] 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/.
[64] Specter, *supra* note 76.

There appears to be a myriad of CRISPR applications in the plant world, and agricultural companies are already on board.[65] 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.[66] DuPont Pioneer has announced plans to begin selling seeds made with CRISPR technology within five years.[67]

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.[68]

The story of who invented the use of CRISPR for gene editing focuses on two research groups.[69] One research group was led by Dr. Jennifer Doudna at the University of California, Berkeley.[70] 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.[71] The second research group was led by the laboratory of Dr. Feng Zhang of The Broad Institute of MIT and Harvard.[72] In early 2013, Dr. Zhang published research demonstrating that CRISPR could be used to modify human genes.[73]

The history of the patent applications arising from both Dr. Doudna's group and from Dr. Zhang's group is more complicated.[74] In March 2013, Dr. Doudna filed a patent application regarding the general CRISPR-Cas9 system, which included a whopping 155 claims.[75] 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).[76]

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.[77] 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).[78] 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

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[65] Talbot, *supra* note 73.
[66] *Id.*
[67] Specter, *supra* note 76.
[68] Otto, *supra* note 77.
[69] Specter, *supra* note 76.
[70] *Id.*
[71] *Id.*
[72] *Id.*
[73] Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCI. 819, 822 (2013); *see also* Specter, *supra* note 76.
[74] *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/.
[75] U.S. Patent Application No. 13/842,859 (filed Mar. 15, 2013) (priority date May 25, 2012).
[76] U.S. Patent No. 8,697,359 (filed Oct. 15, 2013) (issued Apr. 15, 2014).
[77] Sherkow, *supra* note 88.
[78] *Id.*

advancement of human disease therapeutics.[79] 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.

As filed, the two patent applications can seemingly be distinguished.[80] Dr. Doudna's patent application contained language that could be interpreted to limit the claims to apply CRISPR only to *prokaryotic* cells.[81] In contrast, Dr. Zhang's application claimed a method of performing CRISPR editing in *eukaryotic* cells.[82] 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.[83] 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.[84]

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.[85] The purpose of an interference proceeding is to determine which party was actually the first to invent a particular claimed technology.[86]

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.[87] 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.[88] In contrast, 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.[89] 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.

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[79] *Id.*
[80] *Id.*
[81] '859 Patent Application ("The present disclosure provides genetically modified cells that produce Cas9; and Cas9 transgenic non-human multi-cellular organisms.").
[82] '359 Patent.
[83] 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).
[84] *Id.* at 1.
[85] *Id.*
[86] *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.
[87] 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.
[88] 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.
[89] *Id.*

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.[90] 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.[91] 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.[92]

However, the battle over CRISPR patent rights is far from over. The decision was appealed to the Federal Circuit and remains pending on appeal at the current time. 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.[93]

In the wake of the USPTO's decision, both Dr. Doudna and Dr. Zhang were allowed to maintain ownership of their respective patents.[94] 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.[95] If researchers are compelled to obtain a license from both entities, the cost of commercializing CRISPR technology may ultimately increase. 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 methods that may be outside the scope of the claims of *both* the Doudna and Zhang patents.[96]

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.

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.[97] 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

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[90] *Id.*
[91] *Id.*
[92] *Id.*
[93] 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.
[94] *Id.*
[95] *Id.*
[96] *Id.*
[97] *See infra* Part I.

the natural, unmodified product.[98] Alternatively, the second view is a *process-focused* approach that emphasizes review of the actual process by which the GMO is produced.[99] 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.[100]

In the United States, there is no federal legislation specifically directed to review GMOs.[101] 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 Regulation of Biotechnology, published in 1986.[102] 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."[103]

The process of regulatory review and approval varies depending on the type of GMO.[104] 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)."[105] 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."[106] 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)."[107]

Compared to other countries, regulation on GMO development in the United States is relatively favorable. For the U.S., GMOs are very important to the biotechnology industry from an economic standpoint. For example, the U.S. leads the world in producing genetically modified crops. 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).[108] Furthermore, the majority of several different types of crops grown in the U.S. are now comprised of genetically engineered varieties.[109] 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.[110]

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[98] S.J. Mayer, *The Regulation of Genetically Modified Food*, *in* 13 BIOTECHNOLOGY 91 (Horst Werner Doelle et al., eds., 2009).
[99] *Id.*
[100] *Id.*
[101] *Restrictions on Genetically Modified Organisms: United States*, LIBR. OF CONGRESS (Jun. 9, 2015), https://www.loc.gov/law/help/restrictions-on-gmos/usa.php.
[102] *Id.*
[103] Emily Marden, *Risk and Regulation: U.S. Regulatory Policy on Genetically Modified Food and Agriculture*, 44 B.C. L. REV. 733, 738 (2003).
[104] LIBR. OF CONGRESS, *supra* note 115.
[105] *Id.*
[106] *Id.*
[107] *Id.*
[108] CLIVE JAMES, INT'L SERV. FOR THE ACQUISITION OF AGRI-BIOTECH APPLICATIONS, BRIEF 44: GLOBAL STATUS OF COMMERCIALIZED BIOTECH/GM CROPS 7 (2012). https://www.loc.gov/law/help/restrictions-on-gmos/usa.php
[109] *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).
[110] *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.[111]

As of 2010, the EU considers all GMO crops to be "new foods."[112] 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.[113] 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."[114] If accepted, the proposal is then either adopted by the European Commission or is passed on to the Council of Agricultural Ministers.[115] 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.[116] 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.[117] This risk assessment includes evaluations to the molecular characterization of the GMO crop, its potential toxicity, and also its potential to impact the environment**.**[118] Each GMO that is approved must be reassessed every 10 years.[119] 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.[120] In other words, even after garnering an approval in the EU, the GMO crop is still subject to multiple layers of regulatory review.

B. 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.[121] 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.[122] In particular, one proposal was directed to regulation of "intentionally altered" DNA in animals.[123] According to this draft proposal, the

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[111] John Davison, *GM plants: Science, Politics and EC regulations*, 178 PLANT SCI. 94, 94 (2010).
[112] *Id.*
[113] *Id.* at 95.
[114] *Id.*
[115] *Id.*
[116] *Id.*
[117] EFSA, http://www.efsa.europa.eu/ (last visited Mar. 4, 2017).
[118] *Genetically Modified Organisms,* EFSA, https://www.efsa.europa.eu/en/topics/topic/genetically-modified-organisms (last visited Mar. 4, 2017).
[119] *Id.*
[120] *Monitoring Plans and Reports*, EFSA, http://ec.europa.eu/food/plant/gmo/post_authorisation/plans_reports_opinions_en (last visited Mar. 4, 2017).
[121] 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.
[122] *Id.*
[123] *Guidance for Industry – Regulation of Intentionally Altered Genomic DNA in Animals*, FDA (Jan. 2017), *available at*

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.[124]

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.[125] Furthermore, the inclusion of an "'intent"' element in the proposed regulation was also questioned.[126] 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.[127] "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."[128]

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.[129] 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.[130]

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.[131] 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.[132] 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.[133]

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.[134] The gene editing to create the polled animal inserts a gene from naturally hornless beef cattle into a breed of the

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https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf.

[124] *Id.*

[125] Maxmen, *supra* note 143.

[126] *Id.*

[127] *Id.*

[128] *Id.*

[129] *Id.*

[130] *Id.*

[131] 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.

[132] Maxmen, *supra* note 143.

[133] *Id.*

[134] *Id.*

same species used in milk production.[135] As discussed previously, this process could ease animal welfare concerns associated with the removal of horns via burning, cutting, or chemical techniques.[136]

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."[137] However, with the uncertainty surrounding the 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.[138] 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.

C. Regulation of CRISPR Plant Applications

In the U.S., plants with genetic modifications or genetic editing are regulated by the USDA.[139] 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.[140] 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.[141] 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%.[142] 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.[143]

Furthermore, the USDA has also determined that other gene-edited plants (including corn, potatoes, and soybeans that have been edited using TALENs instead of CRIPSR) do not require evaluation, according to existing regulations.[144] This decision offers hope to companies and researchers

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[135] *Gene-editing Options,* THE CATTLE BUSINESS WEEKLY (Jan. 25. 2017), http://cbw60.1upprelaunch.com/Content/Headlines/-Headlines/Article/Gene-editing-options/1/1/8660.
[136] *See supra* Part III B.
[137] Maxmen, *supra* note 143.
[138] *Id.*
[139] http://www.businessinsider.com/the-us-government-says-crop-edited-with-crispr-wont-be-regulated-2016-4
[140] 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.
[141] *Id.*
[142] *Id.*
[143] 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.
[144] Talbot, *supra* note 73.

pursuing gene-edited crops using CRISPR technology. However, the current regulations are under review and may change in the future.

In March 2018, U.S. Secretary of Agriculture Sonny Perdue issued a statement clarify the USDA's oversight of plants produced via CRISPR.[145] In the statement, Perdue indicated that the USDA has no plans to regulate genome editing when used to produce new plant varieties that are indistinguishable from those bred through traditional breeding methods. This important announcement brought some clarification to parties currently using CRISPR to edit plants.

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.[146] In Canada, products are evaluated according to the new "trait" introduced in the plant instead of the process by which the plant was developed.[147] 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.[148] The jury is still out in China, where authorities have not yet decided whether CRISPR-edited crops will be able to be planted.[149]

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.[150] 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.[151]

However, in July 2018, the Court of Justice of the European Union (Europe's highest court) held that that crops created by gene editing would fall under the strict laws restricting the use of GMOs in Europe.[152] The decision represents a tremendous setback for scientists that are interested in the European market. In the decision, the Court stated that the "risks linked to the use of these new mutagenesis techniques might prove to be similar to those that result from the production and release of a GMO through transgenesis (standard genetic modification)."[153]

The court's decision was met with derision by many scientists. Sarah Schmidt, project coordinator at the Institute for Molecular Physiology in the Heinrich Heine University Düsseldorf, called

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145 https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation

146 *"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.

147 Isaacs, *supra* note 164.

148 *Id.*

149 Talbot, *supra* note 73.

150 *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.

151 *Id.*

152 https://www.agri-pulse.com/articles/11274-eu-court-rules-gene-editing-technique-falls-under-gmo-laws

153 Id.

the decision “the deathblow for plant biotech in Europe,” that “could slam the door shut on this revolutionary technology.”[154] Likewise, Maurice Moloney, CEO at the Global Institute for Food Security in Canada said that the decision represented “a real step backwards for the EU, for innovation and in the wider context, for global food security,” he said. “It will have the consequence of further disrupting world trade in agricultural products at a critical time for world trading policy.”[155]

CONCLUSION

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

[154] https://sciencebusiness.net/news/ruling-gene-editing-crops-threat-innovation-and-future-food-security-scientists-say

[155] Id.

SYNGENTA CASE SETS BARRIERS & BOUNDARIES FOR GENETICALLY EDITED CROP & ANIMAL PIPELINES

Thomas P. Redick[1]

This article addresses the challenges that lie ahead for the latest ground-breaking innovation in agriculture – genetic editing.

I will also outline the current status of and potential impacts from the lawsuits tried and settled against Syngenta for its allegedly negligent disruption the U.S. corn export market to China. While some of those cases against Syngenta are still pending, I will chart the potential barriers that these court decisions and settlements could create for biotech crops down the road. With new tools for plant breeding arriving in the form of genetic editing, the threat of liability could undermine innovation for years to come.

The Syngenta case requires a biotech seed company to seek overseas approvals in a newly broadened, court-defined "major" market for the crop in question. The European Union is a major market for most US crops, and it recently decided to regulate genetic editing as if it were a "GMO" (i.e., a recombinant DNA crop of the first generation of biotech plant breeding).

It is clear that the outcome of this case, which creates a duty of care (under the law of negligence) to seek overseas approval before marketing a new biotech crop, along with the expected steady stream of new laws requiring overseas approval, could create barriers to entry to the future use of all agricultural biotechnology in the United States, including new genetically edited crops and animals.

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I. Agricultural Biotechnology Enters a New Era

Genetic editing has come to agriculture promising new traits created with more speed, lower cost and greater precision than any plant breeding tool to date.

Each past transition in breeding, from hybrids to mutagenesis to recombination and now gene-editing, has had challenges in acceptance. You cannot save the seeds from hybrids and replant them – some growers resented this at first, and there are still corners of the world where hybrid corn is shunned for open-pollinating varieties (often sacrificing higher yields for the "Right to Save Seed"[2]). Some proponents of traditional and organic agriculture,[3] particularly in Europe, continue to promote this outdated, lower productivity approach to plant breeding, sometimes using amusing videos decrying payments of royalties to seed breeders.[4] Concerns expressed about safety and the environment appear overblown, with the possible exception of the resistant crop treadmill that must be managed to maintain the benefits of many crops, insects and other biotech organisms.

In the final analysis, however, there is no denying that patenting gives a company the right to own and license a living thing. As a result, there is no reason to believe that the organic industry will ever drop its objections to the patents and "industrial" biocides that may be associated with genetic editing in agriculture.[5] Using this patenting practice as ground to distinguish genetic

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[2] Janak Rhans Ghose, The Right to Save Seed, Rural Poverty and Environment Working Paper Series, Academia.edu (2005) www.academia.edu/2434248/The_Right_to_Save_Seed . (last visited July 20, 2018)

[3] Seed Sharing Deemed Illegal in the United States, https://www.youtube.com/watch?v=txRUeuuKex4 . (last visited July 20, 2018)

[4] The Right to Save Seed, https://www.youtube.com/watch?v=33DwBp2QTgg

[5] The pipeline of genetically edited crops includes many that will resist commonly used herbicides, for example. See, e.g., Cibus Products, https://www.**cibus**.com/**products**.php (**Cibus** is a growth stage company that is currently in the commercialization phase or late-stage development in sulfonylurea (SU) herbicide tolerant **Canola**, glyphosate tolerant Flax, etc.) . (last visited July 20, 2018)

editing in agriculture from past breeding tools that changed DNA (but only used lesser varietal plant patents), it is now clear, after the EU decision discussed below, that nations around the world may raise trade barriers to genetic editing in agriculture, as they become more familiar with genetic editing and the American way of agriculture.

Many more nations are banning biotech crops while endorsing hybrids and mutagenesis breeding, which means that mid-20th Century innovation is finally being accepted in some corners of the world that missed the "Green Revolution". Such tools account for expanding food production exponentially over the past 100 years, and genetic editing will take its place in further expanding food production as the human population stretches its resource limits in the mid-21st Century.

II. Regulatory Barriers to Entry

Gene editing is new enough to the world that many nations are still working on the issue of whether to require pre-market approval.

a. U.S. Regulation

In the U.S., the 1986 Coordinated Framework for the Regulation of Biotechnology ("Coordinated Framework") focuses on regulating the process of recombinant DNA ("rDNA") plant and animal breeding. At the USDA, however, gene editing of crops, however, falls under a "Am I Regulated" website.[6] USDA has decided not to regulate genetic editing crops unless they carry DNA of a plant pest and since most crops do not carry such DNA sequences, there is no

[6] United State Department of Agriculture, Biotechnology Regulatory Services, Am I Regulated Under 7 CFR part 340? (Jun 30, 2017) https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated. (last visited July 20, 2018)

regulatory hook for USDA to regulate.[7] USDA maintains a list of those crops consulted upon, in its

The biotech crop approval process falls under the jurisdiction of USDA's Biotechnology Regulatory Services ("BRS"), which assesses the environmental impacts of biotech crops. If BRS finds no significant impact after a review of the public comments under NEPA and BRS grants the deregulation petition, the way will be cleared for the developer to commercialize the biotech crop.

The EPA has roles in crops that resist herbicides (to approve herbicide uses and warnings) or pests covered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

The FDA, however, issued proposed guidelines to regulate genetically edited animals under its veterinary drug approval process.[8] This same process was used to approve the Aquabounty® AquAdvantage® Salmon, which encountered many delays before approval (and saw an import ban crop up in the US after approval which prevented sale to Americans).[9] There

[7] Isasi1, Keiderman & Knoppers, Editing policy to fit the genome? 22 Science 351 at 337-339 (Jan 2016) Vol. Issue 6271, DOI: 10.1126/science.aad6778

[8] Sarah Zhang, The FDA Wants to Regulate Gene-Editing That Makes Cows Less Horny: What happens when new technology meets old laws, The Atlantic (January 20, 2017) https://www.theatlantic.com/science/archive/2017/01/the-fda-wants-to-regulate-gene-edited-animals-as-drugs/513686/; See Also, U.S. Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine, Draft Guidance for Industry Regulation of Intentionally Altered Genomic DNA in Animal #187, (January 2017) available at https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf (last visited July 25, 2018)

[9] Brady Dennis, FDA bans imports of genetically engineered salmon — for now, Washington Post (January 29, 2016) online at https://www.washingtonpost.com/news/to-your-health/wp/2016/01/29/fda-bans-imports-of-genetically-engineered-salmon-for-now/?noredirect=on&utm_term=.9f04108d071d (last visited July 31, 2018)

may be some apparent disagreement between USDA and FDA over who should regulate gene-edited animals.[10]

b. International Regulation

The European Union's High Court of Justice in July 2018 decided to regulate crops and other organisms produced through genetic editing as if they were a "GMO" under its long-standing "precautionary approach" to regulatory approval. This means that approval times will take several years, sometime longer, for crops to be approved in the EU after being okayed in by North American nations.

The EU's 'precautionary approach" is the law followed by the 171 nations that are parties to the Cartagena Protocol on Biosafety ("CPB"). These parties will meet again for the ninth time (COP-MOP 9) in November 2018 in Egypt, and they will address how to develop their unified approach to genetic editing, which falls under a "synthetic biology" descriptor in this international multilateral environmental agreement. Since the US, Canada, Australia, Argentina and other grain exporting nations are not signatories to the CPB, they cannot block consensus on any attempt by these parties to follow the lead of the EU, which is in many instances a key trading partner and source of foreign aid (e.g., in parts of Africa, where the EU's influence on GMO policy is notably strong).

Canada regulate all "novel foods " and includes genetic editing in that category. This encompasses those crops created using non-rDNA methods. For example, both herbicide-resistant crops created using older (chemical-radiation) or newer (genetic editing) forms of mutagenesis would be regulated. It is worth noting that those older forms of plant and animal

[10] Marc Heller, Agencies clash over biotech livestock, E&E News, (April 19, 2018) available at http://www.sciencemag.org/news/2018/04/us-agencies-clash-over-who-should-regulate-genetically-engineered-livestock (last visited August 7, 2018)

"mutagenesis" breeding arguably carry greater risks of the "pleiotropic" sort raised by activists, who see risks in off-target effects in genes (the adverse nature of which remain unlinked to health concerns). Since many of these crops have similar ecological effects (e.g., there are mutagenic, r-DNA and genetically edited crops with herbicide resistance, all of which can outcross to wild relatives or cause problematic herbicide-resistant weeds to develop after widespread use), Canada's regime at least has a consistent approach to similar risks.

Europe has recently decided to apply its "precautionary" regulatory test to these newer forms of mutagenesis plant breeding.[11] Sweden, Finland, Belgium and the UK had pre-empted the European Court of Justice ruling by greenlighting field trials of gene-edited plants outside the scope of EU GMO law. "these field trials are now illegal." [12] and many other nations in Asia and Africa are likely to follow its lead. Notwithstanding the lack of any scientific theory to suggest serious health threat from crops and animals created using this technology, activists have nevertheless asserted that "the behavior of synthetic biological systems is inherently uncertain and unpredictable, yet the precautionary principle is not guiding research and development of synthetic organisms. Risk assessment protocols have not yet been developed to assess the potential ecological risks associated with synthetic biology."

The international regulatory treaty that allows nations to follow the EU is the Cartagena Protocol on Biosafety ("Biosafety Protocol"), which regulates the release and use of "living modified organisms," also known as genetically modified organisms ("GMOs"). Gene-edited

[11] Jeff Cronin & Ariana Stone, European Union Issues Crucial Ruling on Regulating Gene-Edited Organisms as GMOs (July 26, 2018) https://cspinet.org/news/european-union-issues-crucial-ruling-regulating-gene-edited-organisms-gmos-20180726 (last visited July 20, 2018)

[12] Press release, New GMOs cannot escape testing and labelling under EU law, EU court rules, Greenpeace (July 25, 2018) http://www.greenpeace.org/eu-unit/en/News/2018/New-GMOs-cannot-escape-testing-labelling-under-EU-law-EU-court-rules/

crops would be considered products of "synthetic biology". The parties to the Biosafety Protocol are calling genetic editing a form of "synthetic biology" and will certainly take up the question of how to regulate genetic editing when they hold their next meeting in 2020, now that the EU (a key party) has decided to regulate genetic editing in agriculture as if it were "GMO" technology. NGOs in opposition to old biotech breeding consider these new plant breeding methods to be "GMOS" like their predecessors, not mere "mutagenesis" (which the organic industry embraces form of chemical or radiation mutagenesis, but shuns more precise genetic editing with its relatively minimal off-target effects to target plant DNA).[13]

As part of the implementation of this law, nations that are parties to the Biosafety Protocol enact legislation, such as the European Traceability Directive, that impose zero-tolerance for the import of any GMO that lacks regulatory approval. More nations are imposing regulatory approval requirements as the Biosafety Protocol is implemented. Any biotech crop that could be exported may also require approval in many of these overseas markets. See Appendix A for a chart compiled from various online regulatory sources, listing approaches being taken in various nations for various types of genetic editing (e.g., Oligo-directed mutagenesis or ODM is the tool used by Cibus San Diego for its genetically edited canola, which is widely marketed in the US and Canada).

For innovators in agricultural biotechnology, these approval requirements for overseas markets can create a barrier to their entry. For example, the new biotech potato that the USDA approved for J.R. Simplot Company, known as the Innate™ potato, may require market approval for export to Japan to avoid causing another costly recall of potato chips in Japan, where regulatory approval and genetically-modified ("GM") food labeling could complicate the

[13] Stratfor, How the EU's Stance on Gene Editing May Evolve, (Jan 29, 2018) https://worldview.stratfor.com/article/how-eus-stance-gene-editing-may-evolve (last visited July 23, 2018)

marketing of any foods containing a biotech potato. Simplot's Innate™ potatoes are "cisgenic," meaning that the genes used to transform are from the same species—wild and commercial potatoes. Simplot applied for approval in China, South Korea, Taiwan, Malaysia, Singapore and Mexico, and plans to apply in the Philippines for its first-generation disease-resistant Innate™ potato.[14]

Other genetic editing companies, like Cibus with its genetically edited canola, are getting Canadian and US approval and waiting to see what the Biosafety Protocol will do next, in terms of precautionary regulation.

At the Annual meeting of the Agricultural & Applied Economics Association, the speakers discussed the economic impacts of the EU's decision to regulate, which may spread to up to 100 export markets for soybeans. The entire cost of seeking compliance for a biotech crop was estimated at a range from $7,060,000 to $15,440,000 [15]and most or all of that cost may now be placed upon genetic editing companies who want to market their crops without undue liability risk.

These overseas regulatory approvals, moratoria and other trade barriers to agricultural biotechnology, including genetic editing in agriculture, have demonstrated their power to cause the common law courts in the United States to wake up, take notice, and impose liability on aspects of marketing crops that are fully approved for sale in the US with no federally-imposed restrictions regarding their potential impact on exports.

[14] John O'Connell, Simplot's Innate GMO bruise-resistant potatoes approved for sale in Japan Capital Press, (September 12, 2017) https://geneticliteracyproject.org/2017/09/12/simplots-innate-gmo-bruise-resistant-potatoes-approved-sale-japan/ (last visited July 23, 2018).

[15] Nicholas Kalaitzandonakes, Julian M Alston & Kent J Bradford, Compliance costs for regulatory approval of new biotech crops, Nature Biotech (2007) available at http://www.plantsciences.ucdavis.edu/bradford/Kalaitzandonakes-Compliance%20costs-NBT-2007.pdf (last visited August 9, 2018).

It is worth noting that the USDA has considered such economic impacts, as the National Environmental Policy Act requires of all federal agencies. It has not, however, managed to have "occupied the field" enough to preempt state tort law awarding growers damages for such economic impacts.

III. Liability Precedents to Syngenta's Case

This section briefly addresses the mass tort cases that lead up to a finding that export-related trade disruption can be grounds for a negligence trial. In all of these preceding cases, the questions arose from releases of crops that lacked (or had revoked) approval in the U.S.

The scope of liability for biotech crops has been determined in three stages over the past 15 years. After Starlink® corn recognized a claim for nuisance and negligence arising from a physical injury and regulatory violation that led to a U.S. recall, Liberty Link® rice trials awarded damages based on that precedent for disruption of major markets overseas (mainly the EU) from a rice crop lacking US approval at time of commingling. Syngenta's China case would impose liability for failing to foresee the emergence of a major market and get approval there before allowing Viptera, pending China approval, to commingle in the US corn market.

a. Starlink Corn

The Starlink corn precedent took the first step towards creating biotech seed company liability for failing to foresee the emergence of a major market and get approval there. The court decisions and settlements arising from the sale of Starlink corn by Aventis Crop Sciences USA's predecessor, AgrEvo USA, established that economic injuries could be recovered after commingling of corn that was deemed a "physical injury" to property, including growers' lost

profits. Since the EPA revoked approval for this crop and declared Starlink corn a potential health risk, it was subject to a nationwide and international recalls, with significant disruption of trade.

Starlink corn set the stage for biotech seed company liability by recognizing claims for nuisance and negligence arising from a company's failure to obtain regulatory approval in overseas markets. Damages paid in settlement were calculated based on the price impacts to commodity corn on the Chicago Board of Trade.

b. Liberty Link Rice

This liability risk was expanded to include economic impact from lack of overseas approval in the LL Rice cases. In December 2011, Bayer AG (the German parent company of Bayer Cropsciences) announced that enough growers had signed its proposed $750 million settlement with U.S. rice farmers to confirm that it will compensate them for loss of export rice markets. The decision in LL601 Rice established that negligence could apply to crops that the US had eventually approved--but the EU and other major markets had not. This finding of "contamination" from economic impacts was reinforced by language used in a 2010 Supreme Court decision, as is discussed in more detail below at Section II.G.

Bayer failed to prove that farmers should have simply avoided the brief dip in rice prices and suffered no harm. Bayer also lost its argument that prompt U.S. planting approval after years of unauthorized release (commingling across six states in the rice seed supply) would allow Bayer to bar claims for nuisance or negligence using a federal preemption defense. This ground-breaking court decision, LL601 Rice, is the first decision in the U.S. to follow Starlink and allow mass tort plaintiffs to recover their "economic loss" from the "physical injury" that occurs

from commingling a biotech crop (or other crop, like treated seed) where the crop's only flaw -- or material fact, for consumer fraud claims -- is that it was not approved for export to major markets overseas. The settlements Bayer is entering into in LL601 Rice exceed $1.2 billion, more than the amount reportedly paid in Starlink corn settlements by Bayer's corporate predecessor Aventis. More recent "bellwether" trials raise risks of liability approaching $1.5 billion in the litigation against Bayer Cropscience USA and its parent, Bayer AG, which deemed to be the legal successor to Aventis (despite the efforts of corporate attorneys to structure the sale of Aventis to Bayer as a sale of assets only, leaving liabilities behind).

Commentators have warned that growers may also be liable for disrupting trade if the law evolves in that direction. This negligence-based liability, however, may not stop only with the large biotechnology firm. Farmers or other operators within the broader agricultural supply chain could face similar claims if they were to be found negligent in any future crop commingling litigation. Therefore, farmers should follow basic precautionary strategies, including reading all the fine print listing various crop planting or marketing restrictions. To date, however, this author has not heard of any biotech crops growers in the US being targeted with claims for disrupting trade.

IV. The Liability Bullseye Expands – US & NCGA Approvals Not Preemptive

As counsel to the American Soybean Association and related entities (United Soybean Board, US Soybean Export Council), I assisted in the creation and maintenance of a "Major Market Approval" policy from 1998 to 2016. This policy was created in close consultation with key grain traders, including Archer Daniels Midland, Bunge North America, Cargill, the International Grain Trade Coalition and others. In confidential gatherings held twice a year

(going by various names, e.g., ASA Biotech Working Group), more recently including the NCGA, the policy on major market approval was applied to establish the markets that seed companies had to get regulatory approval in, before they would market new biotech soybeans or corn to growers.

While this might mean 15-20 markets met the "major" designation for soybean exports, the NCGA only required approval in Japan, while also suggesting that approvals be obtained in other major markets. The grain trade adopted its own policies that went beyond both ASA and NCGA, to require approval in major markets one year before planting.

ASA's major market approval policy was intended to set a common law duty of reasonable care in protecting exports to major markets for U.S. soybeans. NCGA, in contrast, would not impose a duty for maintaining regulatory approval in any other markets than Japan.

Syngenta hoped to use, as evidence of its due care, the USDA approval of Viptera and NCGA's request that it be sold without overseas approval in various corn markets. The court denied a procedural motion argument seeking preemption of tort claims due to USDA approval; such preemption of tort claims is getting rarer in US litigation after the Supreme Court rejected FIFRA preemption in Bates v. Dow, 8) 544 U.S. 431 (2005), 332 F.3d 323, vacated and remanded (2005) making federal preemption unlikely in the Syngenta cases.

V. Factual Background – Syngenta Pays for its Misleading Messages on China Approval

Syngenta commercialized its biotech corn trait, Agrisure Viptera® MIR162 ("Viptera") in the United States starting in 2011. Although Syngenta had obtained regulatory approval for the sale of Viptera in the United States, Argentina, Japan, Canada, and the European Union,

Syngenta's application for importation and cultivation approval from the Chinese Ministry of Agriculture was submitted in March 2010.

Nevertheless, Syngenta told growers that it expected approval from China in March 2012, when it should have known, based on feedback from regulatory agencies in China, that approval would still take a year or two more.[16] Like most nations imposing regulatory approval for biotech crops, China had a zero-tolerance policy on the import of biotech corn traits that had not been approved by the Chinese government. Nevertheless, there is no disputing that China had not made any signals of an intent to buy significant shipments of U.S. corn as of spring 2011 when nationwide planting of Viptera began in the United States.[17]

In late 2011, citing ""market signals" coming from China about its corn needs and anticipated selling corn to China., several major grain trading companies (Bunge and Consolidated Grain & Barge (CGB)) told growers that they would not buy Viptera corn. They cited potential sales of US corn to China.

Despite the concerns of the grain trade and China's increasing need for imported corn, Syngenta continued to market Viptera in the United States in 2012. Syngenta's decision not to wait for Chinese approval had the support of the NCGA and was consistent with industry precedent. For instance, Monsanto launched several new corn traits (MON89034 in the Genuity VT Triple PRO stack and SmartStax with Dow) without waiting for Chinese approvals in 2010, and these traits were grown on more acres than Syngenta's Viptera traits were grown in 2011.

In late 2011, Syngenta sued Bunge in response to the grain trader's decision to reject Viptera by for allegedly attempting to illegally block the sale of the Agrisure Viptera trait. Since

[16] Paul Christensen, Chinese Approval of Syngenta Agrisure Viptera, Seed in Context Blog (February 21, 2012), http://www.intlcorn.com/seedsiteblog/?p=268 (last visited April 28, 2017).
[17] Fisher at 5, supra n. 3. (China imports of US corn dipped below one million metric tons ("1 MMT") from 1.2 MMT in 2009-10 (6th largest) to 980 in 2010-11 (5th largest).

Viptera was sold in compliance with all U.S. regulatory requirements and longstanding industry guidance in the U.S., Syngenta felt it had a legitimate right to sell Viptera corn to willing farmers. After a federal court in Iowa denied Syngenta's request for an injunction and dismissed most of Syngenta's claims, Syngenta dismissed the case in December 2014 following approval of Viptera in China.[18]

Over two years later, China stopped accepting all U.S. corn imports in November 2013 and did not begin importing U.S. corn again until late 2014 after China approved Viptera. Although the adverse economic impact of the 13-month trade disruption is debatable given increase in corn yields over the past few years, in April 2014, a grain trade association issued a report suggesting several billions of dollars in adverse economic impacts had been caused by Syngenta's decision to market corn that lacked approval from China.[19]

VI. Summary of Litigation Against Syngenta

In late 2014 and early 2015, grain traders sued Syngenta seeking compensation for lost export markets (measured in millions of dollars) and growers filed class actions seeking billions of dollars for alleged impacts to corn prices quickly thereafter. The plaintiffs claimed that Syngenta failed to follow industry standards for stewardship to keep Viptera out of the export

[18] Syngenta's decision to ultimately dismiss the case was likely due to the fact that its event was approved in China, and that it would have been hard to prove that a buyer does not have the right to choose not to spend money on crops or other products based on their international regulatory status. Despite the outcome of the case, one should wonder whether Syngenta's decision to sue Bunge made it easier for grain traders to decide to sue Syngenta over trade disruption.

[19] *See* Max Fisher, Lack of Chinese Approval for Import of U.S. Agricultural Products Containing Agrisure Viptera™ MIR 162: A Case Study on Economic Impacts in Marketing Year 2013/14, NAT'L GRAIN & FEED ASS'N (April 16, 2014), http://ngfa.org/wp-content/uploads/Agrisure-Viptera-MIR-162-Case-Study-An-Economic-Impact-Analysis.pdf (last visited July 20, 2018).

distribution channel and falsely told growers that China would approve the trait in 2012.[20] The growers asserted claims based primarily on negligence while the grain traders brought negligence claims and claims under consumer protection statutes. The federal cases ultimately were consolidated in the U.S. District Court for the District of Kansas in Kansas City. Syngenta sought and received a motion to dismiss punitive damages in the Kansas class action before trial.[21]

After dismissing some extraneous claims on summary judgment motions, the MDL court certified the class action. Syngenta's interlocutory appeal of the class certification order was denied.[22] A grower[23] wanting to opt out had to send a letter postmarked by April 1, 2017 to be excluded from the class. The first MDL case against Syngenta went to trial in June 2017,[24] and the jury returned a unanimous verdict for Plaintiffs (i.e., 7,343 Kansas farmers). The jury awarded full damages in the amount of $217,700,000 ($217.7 Million).[25] Syngenta filed post-trial motions to dismiss and appeal the verdict after these motions were denied.[26] Syngenta had

[20] *See, e.g.*, Hadden Farms Inc. v. Syngenta Corp., No. 3:14-cv-03302-SEM-TSH (C.D. Ill. filed Oct. 3, 2014) (class action complaint for damages and injunctive relief), http://www.fien.com/pdfs/IllinoisvSyngenta.pdf ("Syngenta Corn Class Action"). (last visited April 28, 2017).
[21] Todd Neeley, Viptera Trial Ongoing: Ruling Could Limit Punitive Damages, (June 19, 2017) available at https://www.dtnpf.com/agriculture/web/ag/news/article/2017/06/19/ruling-limit-punitive-damages (last visited August 26, 2017).
[22] Tenth Circuit denied Syngenta's Attempt to Appeal the Order on Certification, Syngenta Corn Litigation, (December 8, 2016), available at http://www.syngentacornlitigation.com/2016/12/08/tenth-circuit-denies-syngentas-attempt-appeal-order-granting-class-certification/ (last visited August 26, 2017).
[23] Thomas Capehart, USDA estimates around 440,000 farmers grow corn in the United States. (August 16, 2017) available at https://www.ers.usda.gov/topics/crops/corn/background.aspx (last visited August 26, 2017).
[24] U.S District Judge Certifies Syngenta Corn Case Class Action (Sept. 27, 2016), available at http://www.syngentacornlitigation.com/2016/09/26/u-s-district-judge-certifies-syngenta-corn-case-class-action/; Order and notice at www.syngentacornlitigation.com/wp-content/uploads/2016/12/Syngenta2016_Notice_v5.pdf. (last visited April 28, 2017).
[25] AP newswire, The Latest: Syngenta to Appeal $218M Verdict in Seed Case, U.S. News & World Report (June 23, 2017) available at https://www.usnews.com/news/business/articles/2017-06-23/the-latest-syngenta-to-appeal-218m-verdict-in-seed-case. (last visited August 26, 2017).
[26] Id.

been acquired by China National Chemical Corp ("ChemChina") which recently finalized its $43 billion takeover.

The verdicts and settlements piled up. A jury trial for one Nebraska farmer in April, 2017 settled out for a confidential amount. .[27]

Syngenta has also won a case; a defense verdict for Syngenta was awarded by a state court in Ohio based on the economic loss doctrine defense. As that court explained its verdict, while it found that Syngenta had a duty to prevent "physical harm" to growers, it ruled that the economic loss sought by this class of growers (who did not allege pollen drift) was barred by the "economic loss doctrine" ("ELD"), because "[t]here has been no case from any court in Ohio…to show that Syngenta's duty should extend to economic harm caused by the intended use of its products, and this court declines to invent such a duty."[28] In its post-trial motion to dismiss, Syngenta cites this ELD holding and 'submits that there is a substantial basis for rejecting the conclusion that it was "appropriate for the Court to conclude that a [state] court would apply [the ELD] only . . . when the doctrine's purposes would be served."[29]

Syngenta argued that the very nature of this litigation over the ELD precluded a federal court from reaching decisions on such ELD issues.

> The majority rule holds that an integral part of the ELD is the principle that the doctrine should be applied as bright-line rule without case-by-case inquiries into whether the policies behind the doctrine apply on the facts of a particular case. By predicting that the States at issue here would apply the ELD "only . . . when the doctrine's purposes would be served," Order 24 n. 10, the Order effectively predicts that all twenty-two States would reject the rule of the Restatement, which does not permit "case-by-case inquiry

[27] Margaret Cronin Fisk and Jef Feeley, Syngenta Settles Farmer's Contamination Suit Ahead of Trial, Bloomberg, July 7, 2017, available at https://www.bloomberg.com/news/articles/2017-07-07/syngenta-settles-farmer-s-corn-contamination-suit-before-trial. (last visited August 26, 2017).

[28] Fostoria Ethanol, LLC vs. Syngenta Seeds, Inc., Ohio Court of Common Please, Judgment Awarding Motion to Dismiss, Case No. 15 CV 0323 (June 28, 2017)

[29] In re Syngenta AG MIR162 Corn Litigation, Sygenta's Memorandum in Support of Motion to Certify Order on Motions to Dismiss for Interlocutory Appeal Under U.S. Code, §1292(b),Case 2:14-md-02591-JWL-JPO Document 1082 Filed 10/13/15. (last visited August 26, 2017).

into the policies at issue." Restatement (Third) § 7 cmt. b. At a minimum, such a holding raises substantial grounds for a difference of opinion."[30]

Parallel actions by Cargill, a grain trader, are proceeding to trial state court in Louisiana in September 2018.

Non-class cases are also pending – some growers opted out of the class, perhaps remembering resentment of the "gift card" settlements in the StarLink™ ("StarLink") corn litigation.[31]

Syngenta may choose to wait for various statutes of limitations in key corn belt states to expire to reach a complete settlement of all pending cases. This process could take several years.

III. Can These Syngenta Cases be "Distinguished" and Isolated in Legal Precedential Effect?

Rulings made in this case will define the future boundaries for industry stewardship in all commodity crops, with potential negligence for failing to foresee future disruption of a potentially major export market for corn, soy or other exported agricultural products. For the first time in the history of litigation over biotech crops, a claim for negligence has succeeded against conduct in marketing a crop that had full approval for marketing in the United States disrupted an overseas market causing compensable damages in the form of economic impact. Given the history of similar litigation involving StarLink corn and LibertyLink® ("LL") rice, the pending Syngenta litigation may expand the boundary of common law negligence. While the NCGA did not consider China to be a "major market" that would have required approval before an unrestricted U.S. launch, this Kansas court found that Syngenta had a duty to seek major

[30] Id.
[31] AP Newswire, Modified-Corn Lawsuit Is Settled, N. Y. Times (March 8, 2002) http://www.nytimes.com/2002/03/08/business/modified-corn-lawsuit-is-settled.html (last visited August 26, 2017).

market approval (e.g., China, a major market as defined by the grain trade and this court). While courts have traditionally adapted common law claims to address novel challenges and economic harms occurring in society, this case could cause a seismic shift in biotech crop innovation, shutting down some product lines and limiting others to carefully contained production that does not disrupt trade.

As a result, attorneys will be trying to determine where the line of negligence toward export risks will be drawn in future cases. Given the role of underlying factual scenarios in giving rise to precedent, attorney wondering how to advise genetic editing clients of future liability risk should seek to distinguish their clients behavior from Syngenta's behavior, as recorded in the legal opinions arising from this case.

The conduct of Syngenta involved both erroneous predictions about dates of probable approval and the subsequent failure to get approval.[32] A future biotech seed company that does not overpromise and underdeliver may have better facts than the Syngenta case, and find safe harbor in a duty that has been approved widely in the industry by growers, grain trades and other major stakeholders.

While Syngenta followed the NCGA's guidance in selling Viptera, it also sued a grain trader that dared to post signs at elevators informing growers it would not purchase corn containing any trace of Viptera (Bunge North America cited "market signals" from Chinese buyers and the lack of Chinese approval for its decision to bar Viptera sales to it.)

[32] See, e.g., Syngenta Corn Lawsuit: MIR162 Corn (2018) ("Syngenta misinformed farmers, exporters, and the general public about the potential approval of MIR162 in China. These lawsuits further allege that Syngenta led farmers to believe that approval in China was imminent and that China's failure to approve MIR162 would not impact corn farmers.") https://stromlaw.com/syngenta-corn-lawsuit/ (last visited July 30, 2018)

By following a more widely recognized duty, the company selling something not approved in some overseas markets cannot be held liable for negligence. This will allow the Syngenta cases to be distinguished on their facts, and thereby limit their legal precedential effect.

Plaintiffs' core claim of negligence[33] has survived all motions and could provide the best route to recovery. To prevail on their negligence claim against Syngenta, the plaintiffs will have to prove that Syngenta had a legal duty to avoid disrupting exports to China and that its failure to exercise due care caused plaintiffs to incur actual damages.

In response, Syngenta will argue that it owed no duty to growers or grain traders to wait for approval from China and that segregation for export interests is the growers' challenge, depending on the buyers' needs. In support of its position, Syngenta will likely cite to the National Corn Growers Association's ("NCGA") policy which did not require such approvals before launching Viptera.[34] Syngenta may also seek to rely upon the Biotechnology Industry Association's ("BIO") published standards for stewardship, which discuss the need to seek approval in "major" markets with "functioning" regulatory systems.[35] However, it may be an open question whether the 2011 China export corn market was so minimal that it was not "major" and hence the applicable standard of care would only require approval from Japan.

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[33] *See* Non-Producer Plaintiffs' Third Amended Master Complaint at 93-108, *In re* Syngenta Corn Litig., No. 2:14-md-02591-JWL-JPO (D. Kan. Sept. 19, 2016). Available at http://www.ksd.uscourts.gov/non-producer-plaintiffs-third-amended-master-complaint-doc-2530/.(last visited April 28, 2017).

[34] *See*, NCGA, *Know Before You Grow*, (2015), http://www.ncga.com/for-farmers/know-before-you-grow (last visited May 16, 2015); Biotechnology Industry Organization, EXCELLENCE THROUGH STEWARDSHIP, http://excellencethroughstewardship.org/ (last visited April 28, 2017).

[35] Biotechnology Innovation Organization, Excellence Through Stewardship (2015), http://www.excellencethroughstewardship.org/ (last visited April 28, 2017). (last visited July 30, 2018)

While Syngenta stopped being a member of BIO, it has been a member of BIO's Excellence Through Stewardship (ETS) program since 2008.[36] ETS is a program that BIO members sign up for, which requires companies to engage in stewardship for exports, including analyses of market acceptance. Syngenta allegedly failed to implement stewardship to protect exports to China by segregating Viptera to domestic uses.

As Plaintiffs' counsel attests, it Syngenta recognized the harm threatened by irresponsible commercialization, quoting it as saying: "There have been a number of high-profile cases involving genetically modified varieties . . . and disruption of international shipments of commodity grains such as corn, wheat, and rice."[37]

To defeat negligence claims, Syngenta will also argue that the benefits of getting corn traits into production outweighed the alleged adverse economic impacts. Its experts may claim that lower corn prices in the U.S. were due to high U.S. corn production and were not caused by Chinese rejection of U.S. corn.

B. Voluntary Undertaking

As an alternative basis for a duty, plaintiffs alleged that Syngenta owed a duty to them under the voluntary undertaking doctrine. Many states recognize that a duty can arise when a defendant offers to take action to prevent some harm, but negligently fails to fulfill its "voluntary undertaking" (like a "Good Samaritan"). *See McGee v. Chalfant*, 248 Kan. 434 (1991). If Syngenta offered to render stewardship services but failed to exercise due care in the

[36] Syngenta Corn Allegation, Factual Allegations, http://www.syngentacorncase.com/about-the-case/case-updates-documents/class-action/factual-allegations/ (last visited August 9, 2018)
[37] Id. Citing http://www.syngentafoundation.org/index.cfm?pageID=703.

performance of its stewardship program, it could be liable for the harm caused to the growers and grain traders.

Syngenta has cited its relationship with its seed buyers to reject this duty, stating: "[F]armers don't have any exposure whatsoever to Chinese corn rejection. . .. they sell their corn to the elevator" who sells into a grain trader. Willing growers must decide which buyer gets their corn."[38] Growers who bought Viptera are excluded from the class, and while they may be the ones whose corn commingled, they have not been sued for causing trade disruption.

Syngenta alleges that growers who know of buyers' export-related expectations arguably have a duty to protect their own economic interests. A grower can call Syngenta or check NCGA's "Know Before You Grow" webpage or the International Service for the Acquisition of Agri-biotech Applications ("ISAAA") database for export approval information.

Syngenta's failed efforts to contain its corn could give rise to liability under this "voluntary undertaking" basis for imposing a duty of care. In *McGee v. Chalfant*, the Kansas Supreme Court held that, even in the absence of a special relationship, "the actor may still be liable to third persons when he negligently performs an undertaking to render services to another which he should recognize as necessary for the protection of third persons," as set forth in Section 324A of the Restatement of Torts. *See McGee*, 248 Kan. at 438. Plaintiffs argue that Syngenta voluntarily undertook compliance with the BIO Policy concerning the commercialization of new GM products but failed to protect the China export market.

[38] SYNGENTA, FIRST QUARTER 2014 SALES TRANSCRIPT 28 (2014), available at https://www.syngenta.com/global/corporate/SiteCollectionDocuments/pdf/transcripts/q1-2014-transcript-syngenta.pdf (quoting Michael Mack, Syngenta CEO). (last visited April 28, 2017)

In rejecting this argument, the Court in the Syngenta Corn Class Action agreed with Syngenta, finding that Section 324A cannot apply here. Plaintiffs have not sought to recover for "physical" harm and the Restatement section provides for liability "for physical harm resulting from [the actor's] failure to exercise reasonable care to protect his undertaking," *see* Restatement (Second) of Torts § 324A. Since the Kansas Supreme Court has specifically held that Section 324A "has application only in cases involving physical harm," *Barber v. Williams*, 244 Kan. 318, 324 (1989), and the court found no "physical harm" from the decline in prices (as opposed to actual commingling with particular corn), the Court granted Syngenta's motion for summary judgment with respect to any claim of negligence in which liability is based on any alleged misrepresentation, a voluntary undertaking, a failure to warn, or a duty to recall.[39]

D. Damages

Lastly, Syngenta's experts surely claimed, to no avail, that the lower corn prices were not impacted by loss of the Chinese market for around a year during a time of high U.S. corn production. Syngenta could also say that it had permission to market Viptera, and cite NCGA's policy of only requiring approval from Japan and other markets with functioning regulatory systems and BIO's policy of only requiring approval from Japan and Canada.[40]

As was noted above, on June 23, 2017, the jury rendered a verdict against Syngenta for $217.77 million finding negligence in failing to prevent disruption of the export market for US corn to China.

[39] In Re Syngenta AG MIR 162 Corn Litigation, MDL No. 2591 Case No. 14-md-2591-JWL (Apr. 5, 2017), https://ecf.ksd.uscourts.gov/cgi-bin/show_public_doc?2014md2591-3051 (last visited April 28, 2017).
[40] Todd Neeley, Syngenta Trial Set: Viptera Class-Action Case in June, (Feb. 2, 2017), available at ,https://www.dtnpf.com/agriculture/web/ag/news/article/2017/02/02/viptera-class-action-case-summer. (last visited Apr. 28, 2017).

E. Settlement of Grower Class Actions

In September 2017, Syngenta reached a settlement in pending grower class action cases, ending pending trials in those cases. The terms are not fully disclosed and require court approval, but the amount is reported at up to $1.5 billion. Other pending cases outside the Multi-District Litigation do not appear to be included –for example, pending cases filed by grain traders Cargill and ADM are reportedly outside the scope of this settlement. The settlement awards in this litigation could define the boundaries of tort law in agricultural biotechnology for years to come.

III. Impact on the Biotech Innovation Pipeline

The proliferation of small start-up companies in genetic editing appears to have parallels with the long-standing innovation pipeline for biotech-derived pharmaceuticals. Small companies that lack the massive regulatory staffs and capacity for submitting data of a big biotech seed company (after consolidating, we have Bayer merging with Monsanto to emerge as Bayer, Dow absorbing Dupont to become Corteva®, and ChemChina taking over Syngenta. These "big 3" companies all have access to top-rated germplasm in agriculture, as well as regulatory expertise to offer smaller innovators in genetic editing.

As a result, the EU regulatory move will likely serve as a catalyst for moving products of little genetic editing companies into the hands of big biotech seed companies. This would parallel the biotech pharmaceutical industry, where smaller start-up innovators partnered with larger companies to ensure that the high cost of FDA and any overseas national approvals were paid for by the company with more cash on hand.

IV. Conclusion

The court decisions in these Syngenta cases many send the message that any grower or grain trader seeking a specialized market (e.g., the benefits of export markets) should maintain their own identity preserved production to avoid liability. Any failure to implement such self-imposed measures may lead to economic loss, unless a court decide for the seed company (as the court in Ohio did) and finds this loss cannot be recovered in tort against the seller of a U.S.-approved biotech crop that lacked approval in certain export markets. The decisions in cases to come from various U.S. courts will define the boundaries of tort law in agricultural biotechnology for years to come.

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APPENDIX A

Global Genetic Editing Regulatory Approaches

Country	Status	Case-by-Case	Comments
South America			
Argentina	Final	yes	Consultation required, depends on whether there is any new combination of DNA (transgene)
Chile	Final	yes	Consultation required, depends on whether there is any new combination of DNA (transgene)
Brazil	Final	yes	Consultation required, depends on whether there is any new combination of DNA (transgene)
Colombia	Proposed	yes	Consultation required, depends on whether there is any foreign genetic material
North America			
Canada	product based	yes	Canada does not have "GMO" laws - Uses existing regulatory framework based on novelty as trigger for pre-market assessment - no method itself is regulated; 'Novel' products of biotechnology have traits that are new, absent or outside the range for the organism.
US	In progress	yes (am I regulated?)	The U.S. does not have "GMO" laws but a coordinated framework; USDA has made a number of "Am I Regulated?" decisions.
Other			
Australia	Proposed		Not final. Based on proposed changes to legislation (http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/amendment+proposals-1). Categorization may change in final amendments to legislation. The proposals are intended to provide an interim solution whist broader policy considerations associated with new technologies are being progressed through a policy review (http://health.gov.au/internet/main/publishing.nsf/Content/gene-technology-review).

New Zealand	Uncertain		Currently taking a wait and see approach; previous High Court decision ruled that as currently written, gene editing techniques were not excluded from "new organisms provisions."
FSANZ	Code under review		Food Safety agency for Australia and NZ
Israel	Final	yes	
Europe			
EU	Final	yes, *(EJC) decision SDN, & ODM= "GMOs"*	*Opinion of Advocate General for EJC (1-18-2018); said genetic editing introduces foreign DNA (transgene)*
Spain		Yes	*Dutch proposal before EJC; no other genetic material is introduced into the resulting plant than genetic material from the same plant species or from a plant species with which it can exchange genetic material through traditional breeding methods or rDNA used no longer present.*
Netherlands		Yes	*High Council for Biotechnology Opinion. Depends on whether there is any new combination of DNA (transgene).*
France		Yes	*Federal Office of Consumer Protection and Food Safety (BVL) opinion citing a Central Commission for biological safety (ZKBS) evaluation, since it is a targeted mutation rather than an insertion of foreign DNA.*
Germany		Yes	*Agriculture Committee of Chamber of Deputies opinion*
Italy		yes	*Swedish Board of Agriculture; depends on whether there is any new combination of DNA (transgene)*
Sweden		yes	
Norway	*Proposed*		*Norwegian Biotechnology Advisory Board proposed 3-tiered system: notification, expedited, standard assessment Opinion of Advocate General for EJC (1-18-2018); Depends on whether they introduce foreign DNA (transgene)*