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A Fractured International Response to CRISPR-Enabled Gene Editing of Agricultural Products

By CHRISTOPHER M. HOLMAN*

ABSTRACT

IN 2015, SCIENCE MAGAZINE named CRISPR gene editing technology its "Breakthrough of the Year," and for good reason. CRISPR represents a transformative advance in the ability of biotechnologists to edit genes and genomes in both humans and nonhuman organisms. This article begins with a discussion of recent advances in gene editing, including the development of CRISPR and other sequence-specific nucleases (SSNs), and how this new technology compares to other techniques for genetically modifying agricultural plants such as selective breeding, induced random mutagenesis, and, more recently, the use of recombinant technology to produce transgenic plants. It then turns to the complex and dynamic regulatory framework for genetically modified plants as it exists in the U.S., Europe, and elsewhere in the world, and how the various regulatory regimes are responding to recent advances in biotechnology, and in particular gene editing. The U.S. and many other nations appear to be moving in the direction of less regulation for the products of gene editing compared to transgenic crops produced using earlier technologies, while the European Union (EU) on the other hand has indicated that it will subject the products of gene editing to the same burdensome regulatory regime that has to date constrained the development and utilization of GE crops in Europe.

IN 2015, *SCIENCE* MAGAZINE named CRISPR gene editing technology its "Breakthrough of the Year," and for good reason.[1] CRISPR represents a transformative advance in the ability of biotechnologists to edit genes and genomes in both humans and nonhuman organisms. The implications of human gene editing are, of course, profound, but beyond the scope of this *Holman Report*, which will instead focus on the application of gene editing to agriculture, and

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[1]Science News Staff, *And Science's 2015 Breakthrough of the Year Is . . .* , SCIENCE (Dec. 17, 2015), available at https://www.sciencemag.org/news/2015/12/and-science-s-2015-breakthrough-year (last visited January 3, 2019).

more particularly the regulation of genetically engineered (GE) crops and other agricultural plants produced using a sequence-specific gene editing technology such as CRISPR.

The article begins with a discussion of recent advances in gene editing, including the development of CRISPR and other sequence-specific nucleases (SSNs), and how this new technology compares to other techniques for genetically modifying agricultural plants such as selective breeding, induced random mutagenesis, and, more recently, the use of recombinant technology to produce transgenic plants. It then turns to the complex and dynamic regulatory framework for genetically modified plants as it exists in the U.S., Europe, and elsewhere in the world, and how the various regulatory regimes are responding to recent advances in biotechnology, and in particular gene editing. As explained below, the U.S. and many other nations appear to be moving in the direction of less regulation for the products of gene editing compared to transgenic crops produced using earlier technologies, while the European Union (EU) on the other hand has indicated that it will subject the products of gene editing to the same burdensome regulatory regime that has to date constrained the development and utilization of GE crops in Europe.

TECHNOLOGICAL ADVANCES IN THE GENETIC MODIFICATION OF PLANTS

In 2017, scientific advisory groups in the U.S. and Europe issued reports reviewing the latest technical developments in agricultural biotechnology, including gene editing, entitled, respectively, *Preparing for Future Products of Biotechnology* (the NAS Report) and *Explanatory Note: New Techniques in Agricultural Biotechnology* (the EU Report).[2] These reports proved

[2]National Academies of Sciences, Engineering, and Medicine, *Preparing for Future Products of Biotechnology* (National Academies Press 2017) (referred to hereafter as the NAS Report); Scientific Advice Mechanism: High Level Group (SAM HLG) of Scientific Advisors to the European Commissioner for Research, Science and

useful in the preparation of this section of the article, which describes the advance of techniques for improving agricultural genetics, from selective breeding techniques through the latest developments in gene editing, and the interested reader is encouraged to consult them for further insight into the technologies.

Humans have engaged in genetic engineering since the dawn of agriculture, around 13,000 years ago, selecting and retaining organisms suitable for agricultural use. Cultivated crops and livestock possess dramatically altered traits and characteristics relative to any naturally occurring source organism, and this was the case long before modern biotechnology arose in the latter part of the twentieth century. Random mutations occur naturally, sometimes resulting in an improvement (at least from the perspective of humans) in the organism, and by selective breeding, these traits have been propagated and stacked in agricultural plants and animals. Mutations can consist of changes at a single nucleotide position (point mutations), or sometimes more complex changes, such as major rearrangements in the DNA (inversion, translocation) or deletion of DNA fragments. Over time, selective breeding has provided huge benefits to mankind, but it is subject to significant limitations, including the rarity of beneficial mutations arising spontaneously without human intervention, the difficulty of identifying some beneficial phenotypes, and the length of time it takes to proceed from one generation to the next through conventional breeding of plants and animals.

Around 1920, a major breakthrough occurred when agriculturalists began inducing mutagenesis in targeted organisms through the use of mutagens such as chemicals or radiation, thereby greatly increasing the number of mutations and significantly improving the likelihood that a desirable mutation will arise. Still, there are limits as to the extent to which certain

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Innovation, *New Techniques in Agricultural Biotechnology* (Publications Office of the European Union 2017) (referred to hereafter as the EU Report).

characteristics can arise through mutagenesis even when induced. Furthermore, agriculturalists were limited to traits that could be induced in the gene pools of sexually compatible organisms. Because the mutation events are random, a large number of mutant plants must be generated and screened to identify that rare useful mutation. Plants having desirable mutations will generally also have large number of other uncharacterized mutations, some of which might be detrimental. Agriculturalists use successive rounds of backcrossing with an elite variety in order to eliminate unwanted traits, but due to limitations in conventional breeding, the final products are still likely to carry uncharacterized and perhaps detrimental DNA alterations beyond the specific mutation that provided the desired trait. To date, more than 3,200 different commercially available varieties have been developed worldwide using induced mutagenesis.[3] One well-known example of a product of induced mutagenesis is the pink grapefruit.

The 1970s and 80s saw the developments of new techniques for genetically modifying agricultural products, most notably recombinant DNA technology and techniques for introducing foreign DNA into plant genomes. This allowed for the creation of transgenic plants, wherein a genetic sequence of foreign origin is incorporated into the host plant's genome. By removing the limitation of sexual compatibility, the possibility for genetic enhancement through transgenics greatly expanded the possibility of introducing valuable new traits into plants. Some of the most notable and successful early efforts involved introducing bacterial genetic material into row crops (like soybean, canola, corn, and cotton), conferring resistance to herbicides such as glyphosate or the ability to express pesticides like *Bacillus thuringiensis* (BT) toxin. Other notable examples of transgenic crops produced using conventional transgenic technology include

[3]EU Report, *supra* note 2.

virus-resistant squash and papaya, a non-browning apple, and a potato that is low in polyacrylamide when cooked at high temperature.

In the early days of agricultural biotechnology, the primary means of introducing a transgenic DNA construct into a host plant genome was through the use of *Agrobacterium tumefaciens*, a bacterium that in its natural state transfers tumor-inducing DNA into a host plant genome. Biotechnologists took advantage of the ability of *Agrobacterium* to incorporate foreign DNA into a plant genome by engineering the bacterial DNA to eliminate undesirable tumor-inducing genes and replacing them with genetic material intended for introduction into the host, particularly genes encoding desired traits. Significantly, however, use of *Agrobacterium*-mediated transformation generally results in the incorporation of at least some genetic material of *Agrobacterium* origin into the plant genome, and because *Agrobacterium* is a plant pest, and the U.S. Department of Agriculture (USDA) regulates plant pests, this artifact of the process has historically triggered USDA regulatory oversight of most transgenic crops. Transgenic constructs have also often contained foreign promoter sequences derived from a plant pest, like the widely-used cauliflower mosaic virus (CMV) promoter, which will likewise trigger USDA regulation.

Alternative methods of gene delivery to plants were also developed, including biolistics, which involves coating metal microparticles with DNA and then forcibly shooting those particles into target cells, sometimes resulting in incorporation of the DNA into the plant genome.[4] As a general matter, biolistics was less efficient in introducing foreign DNA than *Agrobacterium*-mediated methods, but could be a useful alternative in some plants that proved refractory to the use of *Agrobacterium*. Biolistic methods of introducing foreign DNA into a plant generally avoid the introduction of plant pest DNA into the host plant, and therefore have generally not triggered

[4]Biolistic gene delivery is sometimes referred to as "microprojectile bombardment," and the device used to shoot the microprojectiles as a "gene gun."

USDA regulation. This can be a significant advantage, and indeed might in some cases have incentivized the use of biolistics rather than *Agrobacterium*.

Although transgenic technology greatly expanded the possibilities for genetic enhancement of plants and animals, allowing the creation of traits like herbicide resistance and endogenous pesticide expression that would have been difficult, if not impossible, to achieve through conventional breeding techniques, the technology has its limitations. One in particular is that the established methods for introducing DNA into the plant genome are random, and the insertion event can occur anywhere in the genome, sometimes two or more times at different locations. The resulting phenotype will vary dramatically depending on exactly where in the genome the insertion occurs (a phenomenon known as position effect) because of the effect of adjacent sequences and because of chromosomal structure at that particular location. The insertion might result in insertional mutagenesis or affect the expression of endogenous genes, in either case creating the potential for unintended effects on the phenotype. The insertion of more than one exogenous genetic construct in the same genome can also cause problems, resulting for example in gene silencing, so agricultural biotechnologists generally select for commercialization a variety having a single copy of the transgenic construct.

Because of the variability in phenotype caused by the random nature of the insertion into the plant host genome, agricultural technologists need to make a large number of transgenic plants incorporating the desired DNA construct and screen for plants having the desired phenotype, a laborious and time-consuming process, particularly if the phenotype can only be observed by growing the plant from seed. Once a transgenic variety with the desired phenotype has been identified, it will typically also have less-than-optimal genetic characteristics that have come along for the ride. Repeated backcrossing with a non-transgenic variety having better

overall genetics is generally necessary to arrive at a commercially desirable plant having the desired transgenic trait in combination with an otherwise strong genetic background. Successfully introducing multiple transgenic changes in a single plant genome is even more difficult, which has limited the ability of agricultural technologists to introduce complex phenotypic traits that require the expression of more than a single transgenic gene.

Recent advances in biotechnology have provided agricultural biotechnologists with new tools and techniques that to a large extent overcome the shortcomings of conventional transgenic technology and have opened the door to a new generation of genetically modified agricultural products. Most notable are the sequence-specific nucleases, which allow for targeted modification of plant genomes at a specific nucleic acid sequence, and in principle allow for modification at a single and defined target site in the plant genome. Site-directed genome modification also greatly facilitates the introduction of multiple, precisely defined genetic changes in the genome of a plant without introducing the deleterious ancillary genetic modifications typical of conventional breeding and earlier transgenic techniques.

The first sequence-specific nucleases to be applied to agriculture were the meganucleases, followed by zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs). The general utility of these nucleases was limited by the fact that they all recognize the specific target DNA sequence through an interaction between a protein and the target DNA sequence. Due to the inherent difficulty of reengineering a protein to specifically recognize a different DNA sequence, these nucleases could not be readily modified to target a specific DNA sequence of interest, and as a practical matter, their use was primarily limited to modifications at a single genetic locus.

This significant limitation was overcome by the more recent discovery and characterization of the clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 nuclease system, which recognizes its target DNA sequence through an RNA-DNA interaction.[5] Because RNA is a nucleic acid, it is much more amenable to modifications that reengineer CRIPSR to target any genomic DNA sequence of interests. The CRISPR-Cas9 nuclease system has been shown to function in many organisms, including plants and animals, and is being used to specifically introduce multiple genetic modifications into a single genome. The ability to target integration to a specific location in the genome is advantageous because the location can be targeted in such a way as to induce the desired level of expression of the genetic change while minimizing undesired effects on the phenotype due to effects on neighboring genes.

Sequence-specific nucleases like CRISPR can be used to introduce a variety of types of genetic modifications, including point mutations at a single nucleotide position, deletions of a targeted stretch of sequence, or introduction of foreign DNA. Some products produced using SSNs, such as single point mutations, deletions, or introduction of genetic material from a sexually compatible species, will be indistinguishable from plants that could have arisen spontaneously in nature through mutation or through induced mutagenesis and conventional breeding. On the other hand, SSNs can be used to produce transgenic crops incorporating foreign DNA from a non-sexually compatible organism, and in that sense, these products will be indistinguishable from transgenics produced using established technologies. Transgenic plants produced using gene editing will generally not incorporate foreign pest DNA, which is significant in terms of regulation, particularly in the U.S. where, as discussed below, the USDA has interpreted its authority to regulate transgenics as limited to those incorporating foreign pest

[5]J.A. Doudna and E. Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 12580 (2014).

DNA, or resulting in some likelihood of the host plant becoming a pest. In some cases, exogenous DNA will be incorporated into intermediate products of genome editing, but excised from the final product, which is likely in some cases to greatly reduce the regulatory burden.

Much has been made of the potential for CRISPR technology to open the door for genome editing of a wide variety of organisms, including humans, and the discovery of CRISPR was no doubt a landmark achievement in the advance of biotechnology. But further advances in gene editing seem inevitable. For example, non-Cas9 nucleases had been recently described for CRISPR genome editing.[6] Other gene editing approaches are emerging, including multiplex automated genome engineering (MAGE), which permits multisite genome modifications through hybridization of synthetic oligonucleotides during DNA replication.[7]

All of the techniques for genetically modifying organisms described above, including conventional breeding techniques, have the potential for unintended consequences, and much of the rationale behind regulating GE crops is a concern that some unintended effects could be detrimental to the environment or to the health and safety of humans and animals consuming the product. Unintended effects could result, for example, from disruption or alteration of the plant genome that are ancillary to the modification conferring the desired trait characteristic. However, there is every reason to believe that the products of the latest generation of agricultural biotechnology techniques, particularly genome editing using SSNs, will be less likely to cause unintended effects than either conventional breeding technology or first-generation transgenics.

Conventional breeding, particularly when used in conjunction with induced mutagenesis, is prone to the introduction into the plant's genome of multiple random mutations of generally

[6]B. Zetsche *et al*., *Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, 163 CELL 759 (2015).
[7]NAS Report, *supra* note 2, at 30; *see, e.g.*, M.J. Lajoie *et al*., *Genomically Recoded Organisms Expand Biological Functions*, 342 SCIENCE 357 (2013).

unknown location and effect. Obviously deleterious mutations are often removed by backcrossing with a sexually compatible plant lacking the desired mutation, but as a general matter, conventional breeding techniques are expected to result in an improved product with numerous uncharacterized mutations, any of which could potentially lead to unintended deleterious consequences.

As described above, established recombinant techniques result in the random insertion of the transgenic DNA into the plant genome, and multiple insertion events can also occur at untargeted locations. Depending upon where these insertions occur, deleterious mutations or alteration in expression patterns of the host genome are possible, potentially leading to deleterious consequences. There is also the potential that the introduction of exogenous DNA from a non-sexually compatible organism, such as *Agrobacterium*-derived genetic material or regulatory sequences from plant pests, might have unintended consequences on the transgenic plant. These potential unintended outcomes have been the focus of much of the regulatory review of transgenic crops.

In contrast, because SSNs like CRISPR allow for the targeted insertion of DNA at a known and characterized site in the host genome, it is possible to target the modification to a region that is less likely to disrupt or alter the expression of endogenous genes of the host plant. In principle, this should result in a lower likelihood of unintended deleterious effects in crops produced using modern genome editing technology compared to earlier techniques for genetic modification.

This is not to suggest that unintended effects will not occur with the use of CRISPR and its kin. The employment of these technologies does not exclude “off-target” effects, where the modification not only occurs at the targeted site but also at some other location in the genome

with an identical or similar genetic sequence. But such off-target effects should be rare, and in any event, less frequent than comparable off-target effects resulting from earlier technologies. Also, with advances in whole genome sequencing and the availability of whole genome sequences for targeted host plants, it should be feasible to identify and select for plants that have only been modified at the intended target site.

It follows that the safety concerns associated with unintended consequences should generally be less with the products of SSNs compared to earlier transgenics. The EU Report concluded, for example, that while assessments of risk must always be made on a case-by-case basis, genetically and phenotypically similar products derived using different techniques are generally not expected to present significantly different risks. It follows that, as a general matter, an organism whose genome has been edited to introduce a change that could have been achieved through conventional breeding, such as a point mutation, deletion, or introduction of genetic material from a sexually compatible organism, should not be viewed as posing a more significant safety risk than the host of plants that have been developed over the last century using conventional breeding techniques.

Changes introduced through genome editing that could have arisen out of conventional breeding techniques will in many cases be difficult, if not impossible, to detect and identify. With conventional transgenic crops, the presence of transgenic material can often be detected, particularly if the sequence of the exogenous genetic material is known. For example, DNA sequences originating in *Agrobacterium* have been determined and can thus be screened for. However, in the absence of knowledge of a specific genetic modification that has been made, detection of the change will be difficult, if not impossible. Using whole genome sequencing, it is in principle possible to detect a change in the genome relative to some reference “unedited”

genome. But in the case of a point mutation or other genetic modification that could have arisen naturally or through conventional breeding, while detection of the change is possible, it will generally be impossible to determine if the change was the result of genome editing or the product of conventional breeding—that is, unless whoever is doing the analysis is provided with prior information as to a specific modification that was produced using genome editing.

Numerous exciting and truly transformative applications of genome editing are currently being pursued around the world. CRISPR is anticipated to open the door for creating improved crops that will allow farmers to do more with less inputs, *i.e.*, less water, less fertilizer, and less pesticides, thereby providing not only substantial economic benefit but also benefits to food security and the environment.[8] Other anticipated products of genome editing will provide more direct benefits to consumers, by providing more-nutritious, tastier, healthier, more-convenient, and more-varied plant-based food.[9]

THE REGULATORY RESPONSE TO GENE EDITING IN AGRICULTURE

This section of the article looks at the regulatory regimes in the U.S., EU, Canada, and Japan, and how they are responding to the use of gene editing on plants for agricultural purposes, as well as a recent statement by the World Trade Organization (WTO) addressing the issue

[8]NAS Report, *supra* note 2, at 40–44 and references cited therein.
[9]Statement by the EU Group of Chief Scientific Advisors, *A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive* (Nov. 13, 2018) (referred to hereafter as the Scientific Perspective), at 6 and references cited therein, available at https://ec.europa.eu/info/sites/info/files/2018_11_gcsa_statement_gene_editing_2.pdf (last visited Jan. 3, 2019).

The U.S.

Coordinated Framework for the Regulation of Biotechnology

In the 1970s and early 80s, the United States Congress considered legislation specifically aimed at the regulation of products created through the use of biotechnology, but such biotechnology-specific legislation was never enacted. Instead, President Reagan's Office of Science and Technology Policy (OSTP) stepped into the regulatory void in 1986 and published a document, entitled *Coordinated Framework for the Regulation of Biotechnology*, pursuant to which the primary responsibility for regulation of biotechnology products is shared by three federal agencies: the U.S. Department of Agriculture, the U.S. Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA).[10] The Coordinated Framework essentially directs these agencies to regulate the products of biotechnology under non-biotechnology-specific statutory provisions and agency practices that pre-date modern recombinant biotechnology. The Coordinated Framework is intended to protect against risks to human health and the environment that could potentially result from the development, release, and consumption of genetically modified organisms (GMOs). At the time the Framework was put in place, it was thought that an alternative, unitary statutory approach would be infeasible given the very broad spectrum of products obtained through genetic engineering, with uses cutting across the established regulatory jurisdictions of the different agencies. At the time the Coordinated Framework was issued in 1986, it was understood that the regulatory requirements of biotechnology were "expected to evolve in accord with the experiences of the industry and the

[10]Office of Science and Technology Policy (OSTP), Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23302 (June 26, 1986).

agencies, and, thus, modifications may need to be made through administrative or legislative actions."[11]

The Coordinated Framework remains the foundation of the U.S. regulatory approach to the products of agricultural and industrial biotechnology. In an attempt to provide further policy guidance to the agencies, the Framework was updated in 1992. The 1992 Update to the Coordinated Framework clarifies that GMO products should be regulated based on the "characteristics of the organism, the target environment, and the type of application," not on the process by which the GMO was made.[12] This focus on the product, as opposed to the process used to make it, is significant, and stands in stark contrast to the regulatory approach adopted in Europe, where the focus has been more on the process. Still, some regulated entities would argue that despite the Framework's focus on the characteristics of the product, in practice even in the U.S., regulators have subjected products made using transgenic technology to much more stringent and burdensome regulation than would be the case for comparable organisms produced using conventional, pre-transgenic techniques. The 1992 Update to the Coordinated Framework states that "[i]n order to ensure that limited federal oversight resources are applied where they will accomplish the greatest net beneficial protection of public health and the environment, oversight will be exercised only where the risk posed by the introduction is unreasonable."

The following is a summary of the overlapping regulatory authority of the three primary agencies pursuant to their current interpretation of the Coordinated Framework.

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[11] *Id.*

[12] Office of Science and Technology Policy (OSTP), Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products Into the Environment, 57 Fed. Reg. 6753 (Feb. 27, 1992).

USDA. Under the Plant Protection Act (PPA), the USDA is charged with promulgating and enforcing regulations to protect U.S. crops from noxious weeds and plant pests, *i.e.*, insects, pathogens, and other organisms that harm plants. The agency has interpreted its role under the Coordinated Framework as limited to the regulation of GE agricultural products that have been altered by the introduction of genetic material derived from a plant pest, or when the modification of the plant it is deemed likely to render the plant itself a plant pest, which it does through regulations promulgated under the PPA and found at 7 C.F.R. part 340.[13] The USDA's Animal and Plant Health Inspection Service (APHIS) enforces 7 C.F.R. part 340.

The PPA defines a "plant pest" such that it only applies to a plant that is parasitic, such as mistletoe, and thus would not encompass the sorts of commercially relevant plants that have been the subject of transgenic modification, so as a practical matter, USDA's regulatory jurisdiction in the area of GMOs has been confined to plants that have been modified by the introduction of genetic material derived from a plant pest that is not itself a plant, such as a bacterium or virus. Significantly, USDA has up until now chosen not to assert its authority to regulate noxious weeds in the context of GMOs, although, as discussed below, in 2017, the agency published proposed changes to 7 C.F.R. part 340 that would have done just that.

Under 7 C.F.R. part 340, a GE plant is treated as a regulated article if the donor organism, recipient organism, vector, or vector agent used in engineering the organism belongs to one of the taxa listed in 7 C.F.R. § 340.2 and is also considered a plant pest. APHIS regulates the testing, release and commercialization of products falling within its jurisdiction, and can require pre-market testing, risk analysis, and review for environmental impact under the National Environmental Policy Act (NEPA). APHIS may issue a permit for the commercialization of a

[13]Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There Is Reason to Believe Are Plant Pests, 7 C.F.R. part 340.

product that meets the regulatory definition. APHIS maintains post-market oversight in the form of specific requirements on the introduction of the product and through its compliance and inspection programs.

Historically, *Agrobacterium*-mediated transformation was the method of choice for introducing foreign DNA into plants, and as an artifact of the process, the resulting GMOs retained some *Agrobacterium*-derived DNA. *Agrobacterium* is a recognized plant pathogen, and so the presence of its DNA in the products has triggered USDA regulation. The widespread use of regulatory elements derived from plant pathogens, such as the cauliflower mosaic virus (CMV) promoter, has likewise historically triggered USDA regulation of many GMO crops. In the past, as a practical matter, the presence of plant pest DNA in engineered plant genomes has resulted in the USDA having *de facto* regulatory authority over most of the first generation of GMO crops.[14]

As mentioned earlier, however, there are alternative means for introducing foreign DNA into a plant, such as biolistics, that do not result in the incorporation of plant pest genetic material. USDA–APHIS has made the decision not to regulate GE plants engineered through biolistics so long as the resulting crop contains no DNA sequence derived from a plant pest. USDA regulation is often deemed burdensome, particularly by smaller or mid-sized innovators, and this limitation on USDA regulatory jurisdiction has likely incentivized the development and use of biolistics and other alternatives to *Agrobacterium*-mediated transformation.

Developers of GE plants can petition USDA for deregulation of a GE plant. If the USDA decides to deregulate the plant, its release into the environment and commercialization will no

[14]Kerry Grens, *The Unregulation of Biotech Crops*, THE SCIENTIST (Nov. 25, 2015), available at https://www.the-scientist.com/news-analysis/the-unregulation-of-biotech-crops-34450 (last visited Jan. 3, 2019).

longer be subject to USDA oversight. A list of granted and pending petitions for deregulation is available on the USDA website.[15]

EPA. EPA is responsible for protecting human health and the environment. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA regulates field tests and the commercial use of pesticides. Under section 408 of the Federal Food, Drug, and Cosmetic Act (FDCA), EPA establishes the amount of pesticide chemical residues that may be present in food. Pursuant to this authority, EPA provides regulatory oversight of plants that have been genetically modified to express a pesticide, *i.e.*, a biopesticide or plant-incorporated protectant (PIP). For example, some of the most important early GMO crops were engineered to express the Bacillus thuringiensis (Bt) toxin, a pesticide, which triggered EPA regulation. EPA regulates the pesticide substance and related genetic material for human and environmental safety, including the safety of dietary exposures to pesticide residues in human and animal food, *e.g.*, allergenicity. If a crop is genetically engineered to carry a gene for a Bt toxin, EPA requires the developer to verify that the toxin is safe for the environment and conduct a food-safety analysis to ensure that the foreign protein is not allergenic.[16] A pesticide must thus meet two tests in order to be registered—the benefit of using the pesticide must outweigh the risk, and any residues in food (including food for animals) resulting from the use of the pesticide must meet the safety standard of section 408 of the FDCA.

[15]USDA–APHIS, *Petitions for Determination of Nonregulated Status* (updated Oct. 29, 2018), available at https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions/petitions/petition-status (last visited Jan. 3, 2019).
[16]Alejandro E. Segarra and Jean M. Rawson, *StarLink Corn Controversy: Background* (CRS Report for Congress updated Jan. 10, 2001).

If a GMO plant does not produce pesticide, EPA has taken the position that it does not have regulatory authority. Although herbicide resistant plants are not directly regulated, the herbicide itself is.

Under the Toxic Substances Control Act (TSCA) and regulations implementing that statute, EPA also regulates biotechnology products that are new organisms not specifically excluded by the statute (generally those regulated by other statutes). EPA has interpreted its authority under the TSCA as limited to regulation of genetically modified microorganisms, not plants or animals. If a microbe is intergeneric, and is manufactured or processed for commercial production purposes, including research and development (R&D) for commercial purposes, for a use that is not excluded under TSCA, nor otherwise exempt from reporting, it is under EPA's regulatory jurisdiction. EPA has not asserted authority to regulate genetically modified plants that have not been engineered to produce a pesticide, although, as discussed later, it has been suggested that the EPA could choose to interpret the TSCA more expansively and assert regulatory oversight over any genetically modified organism released into the environment that is not regulated by another agency.

FDA. FDA's regulatory role under the Coordinated Framework arises primarily under the FDCA, which charges FDA with the task of regulating the safety of products intended as food for humans or feed for animals. Pursuant to this authority, FDA regulates genetically modified products intended for use as food by humans or animals, including plants, animals, and microorganisms. This encompasses a large percentage of genetically modified agricultural products, both plant and animal. Once these genetically modified products enter the market, FDA is authorized to regulate them for health and safety concerns, and if a genetic modification is

found to result in an "adulterated" product, that product can be removed from the market and sanctions imposed on the company responsible.[17]

Significantly, there is no mandatory pre-marketing approval requirement for food or feed under the FDCA. FDA has, however, instituted a voluntary consultation process through which a company developing a genetically modified food product can consult with the agency prior to market entry to obtain FDA's opinion as to whether the agency sees any safety concerns associated with the contemplated product. These include the potential allergenicity and toxicity of any newly-introduced proteins in food from the plant, whether any newly-introduced substance in food from the plant requires premarket approval as a food additive, and whether levels of endogenous toxicants and important nutrients or anti-nutrients have been changed in a way that is relevant to food safety or nutrition. Although the consultation process is not legally required, FDA reports that, to the best of its knowledge, all GE food crops intended for marketing have been the subject of a consultation or other relevant pre-market processes prior to marketing.

If genetic modification is deemed to create a food additive, then the food additive provisions of section 409 of the FDCA would be triggered. Section 409 does require the pre-market approval of any biomolecule introduced through genetic engineering that is deemed a food additive.

The regulatory burden

Although numerous genetically modified products have successfully made their way through the Coordinated Framework's regulatory regime and entered the market, agricultural

[17]Section 402(a)(1) of the FDCA.

biotechnologists have complained that the process is unduly burdensome on innovators in terms of cost, delay, and unpredictability. This creates a disincentive to the development of new GE agricultural products, particularly for small or mid-sized companies and academic institutions less able to deal with the complex regulatory framework than the large multinational corporations that currently dominate agricultural biotechnology.

As discussed below, there are certain categories of GE crops that, under the current interpretation of the Framework and the agencies' jurisdictional reach, are not regulated by any of the three agencies. At the other extreme, however, some GE crops fall under the jurisdiction of all three agencies. Bt soybean produced using *Agrobacterium*-mediated transformation would be one example, since the product is intended for use as food and has been engineered to incorporate plant pest DNA and express a pesticide.

Agricultural innovators have reported that with respect to some GE crops, there has been uncertainty as to which agency or agencies will assert jurisdiction. For a product that is subject to regulation by more than one agency, the regulated innovator must deal with multiple agencies, whose requirements might be different or even inconsistent, and under circumstances in which it is unclear whether any agency has primary authority. Without an identified lead agency, a regulated entity has trouble knowing which to approach for initial consultation.

It can take a great deal of time for an innovator to achieve regulatory approval for a new GE crop. For example, an article in *The Scientist* describes how it took more than a decade for a company called Okanagan Specialty Fruits to achieved deregulated status from the USDA for its non-browning "Arctic" apple, which relies on the use of cauliflower mosaic virus promoter delivered via *Agrobacterium*-mediated transformation to silence an enzyme that causes

browning.[18] This use of plant pest–derived DNA triggered USDA regulation of field trials and marketing of the product. Field trials were first planted and 2003 and 2005, the company submitted documentation to USDA 2010 requesting deregulation, and it took another five years of review and public comment before the agency announced its decision deregulating the apple. In retrospect, the company's president expressed frustration at how long and costly the process for achieving USDA deregulation was, particularly given the relatively minor genetic change that had been made compared to other approved biotech crops. "For a small, grower-led company like ours (our team had less than five full time employees when we submitted the USDA petition), it was a monumental challenge to go through such a lengthy, costly process to achieve deregulation."[19]

Many would argue that the regulatory delays and expenses on the use of recombinant DNA technology is unduly burdensome and continues to be disproportionate to its risk, and that the opportunity costs of regulatory delays and expenses are formidable. According to a survey completed 2011, the cost of discovery, development, and authorization of a new plant biotechnology trait introduced between 2008 and 2012 was $136 million.[20] On average, about 26 percent of those costs ($35.1 million) were incurred as part of the regulatory testing and registration process.[21] In 2011, the USDA instituted the "Am I Regulated?" process to help seed innovators determine if their products need to go through the full-blown regulatory process, by

[18]Kerry Grens, *The Unregulation of Biotech Crops*, THE SCIENTIST (Nov. 25, 2015), available at https://www.the-scientist.com/news-analysis/the-unregulation-of-biotech-crops-34450 (last visited Jan. 3, 2019).

[19]*Id*.

[20]*Cost of Bringing a Biotech Crop to Market*, CROPLIFE INTERNATIONAL (2011), available at https://croplife.org/plant-biotechnology/regulatory-2/cost-of-bringing-a-biotech-crop-to-market/(last visited Jan. 3, 2019).

[21]*Id.*

providing the opportunity for an initial screening to determine if there is sufficient potential for problems to warrant a closer look.[22]

Gaps within the Coordinated Framework

While there is redundancy under the Framework, conversely, there are significant gaps in coverage whereby some GE products apparently fall outside the regulatory jurisdiction of any of the agencies. For example, none of the three federal agencies would appear to have jurisdiction over a GE plant that is not a plant pest or noxious weed, does not contain plant pest DNA or DNA encoding a pesticide, and is not intended as food for humans or animals or to produce a drug. Examples could include ornamental, silvicultural, and turfgrass crops, or crops used to produce a non-food, non-drug product, like a chemical, fuel, or structural material.

USDA's jurisdictional limitations were identified as far back as 2000 in a National Research Council report and have been discussed in the literature.[23] With the development of new methods for introducing foreign DNA into plants and regulating foreign gene expression that does not involve the use of plant pest DNA, USDA is increasingly coming to the conclusion that it does not have regulatory jurisdiction over recently developed GE plants.

One interesting case that caught the attention of the mainstream media involved a do-it-yourself biotechnology (DIYbio) project that resulted in a genetically engineered bioluminescent plant dubbed the "Glowing Plant."[24] The process used did not result in the introduction of plant

[22]USDA–APHIS, *Am I Regulated Under 7 CFR part 340?* (last modified Dec. 14, 2018), available at https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated (last visited Jan. 3, 2019).
[23]NATIONAL RESEARCH COUNCIL (NRC), GENETICALLY MODIFIED PEST-PROTECTED PLANTS: SCIENCE AND REGULATION (National Academy Press 2000), and J. Kuzma and A. Kokotovich, *Renegotiating GM Crop Regulation*, 12 EMBO REPORTS 883 (2011).
[24]Bob Grant, *Debate Over Glowing Plants Grows*, *THE SCIENTIST* (June 5, 2013), available at https://www.the-scientist.com/the-nutshell/debate-over-glowing-plants-grows-39210 (last visited Jan. 3, 2019).

pest DNA into the product, and it was not intended for use as food or feed, so under the prevailing interpretation of the Coordinated Framework, none of the three agencies had a jurisdictional hook to regulate the public release of the GE plant—which not surprisingly resulted in perceived safety concerns.[25] However, the Glowing Plant project was conceived as the starting point for future modifications by DIY biotechnologists, and its developers encouraged others to further modify the plant's genome using a kit that included *Agrobacterium*-based transformation materials and protocols which, if used, would result in the introduction of plant pest DNA into the resulting product, thereby triggering USDA regulation.

While the Glowing Plant project captured the attention of the popular press, a more commercially significant example of a regulatory blind spot arose in 2011 when the USDA was asked to review the regulatory status of a genetically engineered grass species transformed using biolistics. The agency concluded that it did not have regulatory authority over the product since the engineering did not incorporate plant pest DNA into the grass, and the engineered grass itself was not deemed likely to be a plant pest.[26] And because the grass is not intended for use as food or feed, and does not contain a pesticide, under current interpretation of the Coordinated Framework it does not fall under the regulatory authority of FDA or EPA. According to the NAS Report, between that decision in 2011 and December 2016, more than 40 GE plant products were submitted to USDA–APHIS for a determination as to whether they fell within the regulatory

[25] *Id*.

[26] *See* letter from Michael C. Gregoire, Deputy Administrator, U.S. Department of Agriculture–Animal and Plant Health Inspection Service to Richard Shank, Senior Vice President, Scotts Miracle-Gro Company, concerning confirmation of regulatory status of Kentucky bluegrass (July 1, 2011), available at https://www.aphis.usda.gov/brs/aphisdocs/scotts_kbg_resp.pdf (last visited Jan. 3, 2019).

purview of the agency, and most of them were reportedly determined to be outside the scope of the agency's authority to regulate plant pests.[27]

Recent initiatives to reform and modernize the Coordinated Framework

In July 2015, the Obama administration released a memorandum charging the FDA, EPA, and USDA with the task of *Modernizing the Regulatory System for Biotechnology Products* (the 2015 EOP memorandum). [28] The memorandum notes that while

> the current regulatory system for the products of biotechnology effectively protects health and the environment, in some cases, unnecessary costs and burdens associated with uncertainty about agency jurisdiction, lack of predictability of timeframes for review, and other processes have arisen. These costs and burdens have limited the ability of small and mid-sized companies to navigate the regulatory process and of the public to understand easily how the safety of these products is assured.

The memorandum found it to be imperative that U.S. regulatory system be reformed in a manner that would reduce regulatory burdens on innovators in order to avoid "unjustifiably inhibiting innovation, stigmatizing new technologies, or creating trade barriers," by improving transparency, predictability, and efficiency of the regulation and improving the coordination among the three agencies.

[27]NAS Report, *supra* note 2.
[28]Executive Office of the President (EOP), Memorandum for Heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture, *Modernizing the Regulatory System for Biotechnology Products* (July 2, 2015) (hereafter referred to as July 2015 EOP memorandum).

The 2015 EOP memorandum provides for the creation of a Biotechnology Working Group comprising representatives from the Executive Office of the President (EOP) and the three agencies, and charges the working group with the tasks of: (1) updating the Coordinated Framework to clarify the current roles and responsibilities of the agencies that regulate the products of biotechnology; (2) developing a long-term strategy to ensure that the federal regulatory system is equipped to assess efficiently the risks, if any, associated with future products of biotechnology while supporting innovation, protecting health and the environment, maintaining public confidence in the regulatory process, increasing transparency and predictability, and reducing unnecessary costs and burdens; and (3) in order to inform future policymaking, to commission an external, independent analysis of the future landscape of biotechnology products that will identify potential new risks and frameworks for risk assessment and areas in which the risks or lack of risks relating to the products of biotechnology are well understood.

In response to the third charge, the working group commissioned a report from National Academies of Sciences, Engineering, and Medicine aimed at providing a better understanding of the landscape of future products of biotechnology, which resulted in in the 2017 NAS Report, which concludes:

> While the current regulatory system for the products of biotechnology effectively protects health and the environment, in some cases unnecessary costs and burdens associated with uncertainty about agency jurisdiction, lack of predictability of timeframes for review, and other processes have arisen. These costs and burdens have limited the ability of technology developers, particularly those in small and

> mid-sized companies and in academic research institutions, to navigate the regulatory process and have limited the ability of the public to understand easily how the safety of these products is assured. Accordingly, the costs and burdens have the potential to hamper economic growth, innovation, and competitiveness.[29]

In response to the first two charges, the EOP in 2016 published a *National Strategy for Modernizing the Regulatory System for Biotechnology Products*, which includes a number of commitments from the three agencies for actions and reforms.[30]

In January 2017, the EOP followed up with an update to the Coordinated Framework entitled *Modernizing the Regulatory System for Biotechnology Products: An Update to the Coordinated Framework for the Regulation of Biotechnology*, the first update to the Coordinated Framework in more than 20 years.[31] Significantly, this Update to the Coordinated Framework does not provide for any actual updates or changes to the framework, merely providing clarification as to how the Coordinated Framework has and presumably will continue to be applied, nor does it specifically address gene editing.

The agencies' response to gene editing

This section of the article discusses how the three agencies have responded to the arrival of gene editing of plants for agricultural purposes.

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[29]NAS Report, *supra* note 2.

[30]Emerging Technologies Interagency Policy Coordination Committee's Biotechnology Working Group, *National Strategy for Modernizing the Regulatory System for Biotechnology Products* (Sept. 2016), available at https://www.epa.gov/sites/production/files/2016-12/documents/biotech_national_strategy_final.pdf (last visited Jan. 3, 2019).

[31]EOP, *Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology* (2017), available at https://www.fda.gov/downloads/Safety/Biotechnology/UCM620374.pdf (last visited Jan. 3, 2019).

USDA. Because the new gene editing techniques do not result in the introduction of plant pest DNA into the host, as a general matter, these plants will apparently not be subject to USDA regulation, at least under the USDA's current view of its own regulatory authority. As of 2016, USDA–APHIS had considered several cases of crops engineered with genome-editing technology that caused directed insertions or deletions of one to several bases and determined that the plants are not subject to USDA regulation. Even in cases where plant pest genetic material is used in the developmental stages of a genetically modified product, it will often be possible to remove those from the final product. In these situations, USDA has not required pre-market testing, has not reported a risk finding, nor has it undertaken a NEPA analysis. USDA–APHIS responses to letters of inquiry regarding the regulatory status of proposed GE plants often contain language with recommended actions for developers to ensure that plant pest genetic sequences will not be present in the final product. Genome-edited crops have, however, been found subject to USDA regulation if the final product retains DNA that originated in a plant pest.

One example of a gene-edited agricultural product that was assessed by USDA and found to be outside its regulatory purview is a mushroom engineered to resist browning through gene editing that essentially turned off a gene in mushrooms that produces an enzyme that causes browning, the equivalent of a naturally occurring "null" mutation.[32] Similarly, in 2014 a research team from Iowa State asked USDA whether its disease-resistant rice, produced by gene editing using TALENs technology, would be regulated. Although *Agrobacterium*-based transformation was used as an intermediate step, the final product did not contain any inserted genetic material, and the agency determined that in the absence of any inserted genetic material and no reason to

[32]Emily Waltz, *Gene-Edited CRISPR Mushroom Escapes US Regulation*, 532 NATURE 293 (2016).

believe that the rice would constitute a plant past, the plant is not subject to USDA regulation.[33] USDA warned the Iowa State researchers that GE rice plants from this transformation that retain inserted genetic material would be considered regulated under 7 C.F.R. part 340.

In January 2017, USDA–APHIS published a proposed rule (the "2017 Proposal") for comment that specifically addressed the products of gene editing and that would, if implemented, have significantly changed the manner in which the USDA regulates GE plants.[34] In November 2017, after considering comments it received from the public, the agency withdrew the proposed rule.[35] Nevertheless, it is worth reviewing the 2017 Proposal because even though it was withdrawn, it seems likely that the USDA will ultimately move in the direction charted by the proposal, and in fact the agency issued a statement in 2018 adopting certain aspects of the 2017 Proposal, as discussed below.

The 2017 Proposal states that the agency's 30 years of experience regulating GE crops has provided evidence that most genetic engineering techniques, even those that use a plant pest as a vector, vector agent, or donor, do not result in a GE organism that presents a plant pest risk. On the other hand, the agency notes that the use of new techniques for genetically modifying plants is increasingly resulting in the release of plants that could potentially pose a threat to agriculture, but which are not subject to USDA's regulatory jurisdiction under its current regulations.

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[33]*See* letter from Michael Firko, Deputy Administrator, U.S. Department of Agriculture–Animal and Plant Health Inspection Service to Dr. Bing Yang, Department of Genetics, Development, and Cell Biology, concerning inquiry regarding APHIS position on null-segregant TALEN-mutagenized rice lines as non-regulated articles (May 22, 2015). Available at https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/aphis_resp_isu_ting_rice.pdf (last visited Jan. 3, 2019).

[34]USDA–APHIS, Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms, 82 Fed. Reg. 7008 (Jan. 19, 2017).

[35]USDA–APHIS, Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms, 82 Fed. Reg. 51582 (Nov. 7, 2017).

The 2017 proposal would address the issues identified above by expanding the scope of USDA regulation under 7 C.F.R. part 340 to encompass GE plants that could potentially constitute noxious weeds. As mentioned above, the PPA provides for regulation of noxious weeds, but up until now, USDA's regulations promulgated under the statute have been limited to GE plants that either incorporate plant pest DNA or which could themselves be considered a plant pest (which as a practical matter never happens); GE plants have to date not been regulated as potentially noxious weeds. USDA states that its proposal to expand its regulatory authority to encompass potentially noxious weeds is driven primarily by two consequences of recent advances in agricultural biotechnology, particularly the development of non-*Agrobacterium*-based techniques for introducing foreign DNA into a plant's genome and sequence-specific gene editing.

First, as a practical matter, GE crops have until recently generally been subject to USDA regulation owing to the presence of genetic material from *Agrobacterium* or another plant pest, but with the more modern techniques like biolistics and gene editing that do not result in the incorporation of plant pest–derived DNA the USDA has lost this jurisdictional hook. Secondly, the nature of GE plants is changing with the advances in technology, such that it appears more likely that the GE products of the future could pose a threat as noxious weeds. The original targets for genetic modification were crops like corn, soybean, and canola, plants that are not plant pests and are not likely to be turned into plant pests by the modifications that were being made. But today genetic modifications are increasingly being introduced into plants that are more weed-like in character, such as switchgrass for biofuel production, thereby increasing the likelihood that a genetic modification might result in a plant with a greater tendency towards becoming a weed.

On the other hand, the agency proposes that in the future, GE plants that incorporate plant pest DNA, such as *Agrobacterium*-transformed plants, will be scrutinized more for their potential to be noxious weeds, rather than focusing so much on the plant pest DNA that has been introduced, given the generally safe track record of GE plants produced using *Agrobacterium*-mediated transformation and other established techniques that involve the use of plant pest DNA.

Under the 2017 Proposal, APHIS would begin its regulatory review of a new GE variety by evaluating whether the plant, in its unmodified state, has weedy characteristics, *i.e.*, a plant biologically capable of causing "notable physical injury or damage" to crops. This would serve as the baseline against which to evaluate the genotype of the GE plant. In evaluating the GE plant, APHIS would assess the likelihood that the modifications made to the genome of the plant would alter its ability to cause notable physical harm or injury.

For GE plants that APHIS determines to be weedy prior to genetic modification, APHIS would endeavor to determine whether the plant's weediness has been enhanced to an extent that it has been engineered into a noxious weed. For GE plants that APHIS determines not to possess weedy traits prior to modification, APHIS would endeavor to determine whether weediness had been introduced into the organism through genetic engineering. Finally, in the event that a Federal noxious weed (a subcategory of noxious weeds) is genetically engineered (something that has not occurred to date), APHIS would endeavor to determine whether the GE plant is still a noxious weed and warrants continued regulation.

If APHIS determines that the GE plant is a noxious weed, it would endeavor to gauge the direct or indirect injury or damage it could cause to crops, livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment. APHIS would no longer consider GE organisms to be regulated articles solely

because of the donor, vector, or vector agent used in genetic engineering, thereby focusing its resources on those GE organisms that may present a plant pest and/or noxious weed risk.

Of particular relevance to gene editing, the 2017 Proposal clarifies that USDA regulation under 7 C.F.R. part 340 has and will continue to only apply to an organism that is a "GE organism," defined as an organism developed using "genetic engineering." The proposal would define "genetic engineering" as "techniques that use recombinant or synthetic nucleic acids with the intent to create or alter a genome." The definition explicitly excludes traditional breeding techniques and chemical- or radiation-based mutagenesis, which the agency has never considered to constitute genetic engineering. Note that this only applies to regulation under 7 C.F.R. part 340, and does not restrict other potential bases for USDA regulation.

APHIS would also exclude from its definition of GE organism those that are created using techniques that fall within the scope of genetic engineering, but that could otherwise have been produced using traditional breeding techniques or chemical- or radiation-based mutagenesis. The USDA has concluded that such organisms are essentially identical, despite the method of creation, because while there may be small genetic differences, those differences are not phenotypically observable and these types of changes occur naturally in all organisms. APHIS would also exclude "null segregants," that is, the progeny of a GE organism where the only genetic modification was the insertion of donor nucleic acid into the recipient's genome, but the donor nucleic acid is not passed to the recipient organism's progeny and the donor nucleic acid has not altered the DNA sequence of the progeny.

To summarize, for purposes of the revised regulations, an organism would not be considered a GE organism if:

> (1) The genetic modification to the organism is solely a deletion of any size or a single base pair substitution which could otherwise be obtained through the use of chemical- or radiation-based mutagenesis;
>
> (2) The genetic modification to the organism is introducing only naturally occurring nucleic acid sequences from a sexually compatible relative that could otherwise cross with the recipient organism and produce viable progeny through traditional breeding (including, but not limited to, marker-assisted breeding, as well as tissue culture and protoplast, cell, or embryo fusion); or
>
> (3) The organism is a "null segregant."

APHIS would exclude the first two types of organisms from the definition of GE organism because the organisms could have been produced from techniques that have never triggered USDA regulation under 7 C.F.R. part 340, and that would continue to be excluded from the definition of genetic engineering under the proposed revision to the regulations. The USDA points out that chemical- and radiation-based mutagenesis creates thousands of mutations in a single organism, and most of a plant breeders' subsequent efforts involve eliminating unwanted mutations by repeated crosses and selection, each of which can take months to years to complete. Conversely, using genetic engineering, single base pair substitutions, as well as deletions of differing sizes, can be precisely administered very quickly, avoiding this lengthy process of eliminating unwanted mutations. The resulting organism, however, remains identical to one that could otherwise have been developed using chemical- or radiation-based mutagenesis.

Similarly, traditional breeding techniques may require many generations of crossing to introduce a naturally occurring trait. For example, it can take decades to introduce a disease-resistant trait to apples through traditional breeding techniques. However, genetic engineering can introduce the same trait in a fraction of the time while maintaining all other cultivar characteristics of the apple.

Another rationale behind the first two exclusions is USDA's conclusion that GE plants as a class pose no greater plant pest or noxious weed risk than their counterparts developed through traditional breeding techniques or chemical- or radiation-based mutagenesis. Moreover, the agency deems it both impracticable and unnecessary to regulate plants created through traditional breeding techniques or chemical- or radiation-based mutagenesis for plant pest or noxious weed risk.

The USDA points out that traditional breeding techniques, in the form of deliberate selection and breeding of those plants with desirable phenotypes, have been used since the advent of sedentary agriculture, and nearly every domesticated crop has, at one point, been subject to traditional breeding techniques. Chemical- and radiation-based mutagenesis, in turn, have been used for nearly a century in the development of thousands of commodities, including such commercial products as ruby red grapefruit and many commercial varieties of wheat and rice. If APHIS were to regulate organisms developed through traditional breeding techniques or chemical- or radiation-based mutagenesis, that would entail the regulation, at least provisionally, of almost every commercially available human or animal food crop, which the agency would find impracticable.

Furthermore, USDA states that the regulation of such organisms would fail to take into adequate consideration that phenotypic traits that could increase the plant pest or noxious weed

risk posed by a plant tend to also adversely impact its vitality, uniformity, or commercial viability. For example, a mutation caused by chemical- or radiation-based mutagenesis could render a plant more susceptible to certain viroids or pathogens and able to transfer this increased susceptibility to sexually compatible relatives, and thus increase the plant pest risk associated with the plant. However, it would also directly adversely affect the plant's vitality. For these reasons, farmers and developers have long bred out unwanted phenotypic traits that arise as the result of traditional breeding techniques and/or chemical- or radiation-based mutagenesis, and planted and/or commercialized the most phenotypically desirable plant produced using such techniques.

Regarding the proposed exclusion for null segregants, *i.e.*, the progeny of GE organisms where the only genetic modification was the insertion of donor nucleic acid into the recipient's genome, but the inserted donor nucleic acid is not passed to the recipient organism's progeny and has not altered the DNA sequence of the recipient organism's progeny, the 2017 Proposal notes that traits can sometimes be introduced by genetic engineering into breeding lines to simplify breeding without altering the DNA sequence of progeny, and that such traits can be eliminated with a simple cross and are no longer present in the final organism. An example of the use of such techniques to facilitate traditional breeding would be the introduction of certain genes into trees solely to reduce the time to flowering, thereby speeding up a tree-breeding program. In this example, the progeny do not contain the early flowering gene and their DNA sequence has not been altered by the early flowering gene. Because the DNA of the progeny is no different from the DNA of the recipient organism prior to the use of genetic engineering, APHIS does not consider the progeny to be GE organisms for purposes of the proposed regulations.

As noted above, in November 2017, after considering comments it received from the public, the agency withdrew the proposed rule.[36] Perhaps the change in presidential administrations had something to do with the decision. In any event, in March 2018, USDA issued a statement adopting some aspects of the 2017 Proposal by announcing that the agency will not assert regulatory authority over genetically altered plants so long as they could have been developed in the alternative through traditional breeding methods, such as cross-breeding or selecting for desirable properties.[37] The agency noted that genome editing allows breeders to introduce new traits more precisely, and at a faster rate. "With this approach, USDA seeks to allow innovation when there is no risk present," U.S. Secretary of Agriculture Sonny Perdue said in the statement. "Plant breeding innovation holds enormous promise for helping protect crops against drought and diseases while increasing nutritional value and eliminating allergens." The statement does not say anything about gene editing that results in incorporation of foreign DNA into the genome.

EPA. As explained above, under FIFRA EPA regulates GE crops that have been modified to express a pesticide, which EPA refers to as a plant-incorporated protectant (PIP). FIFRA specifically exempts "pesticidal substances produced through conventional breeding of sexually compatible plants," and EPA has exempted from FIFRA requirements PIPs that occur naturally in the plant or are moved through conventional plant breeding.[38] This raises the question of whether EPA would assert regulatory authority in a case where a pesticidal activity, such as disease resistance, has been introduced through gene editing, particularly if the

[36] *Id*.
[37] Press Release, USDA, Secretary Perdue Issues USDA Statement on Plant Breeding Innovation (Mar. 28, 2018), available at https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation(last visited January 3, 2019).
[38] 40 C.F.R. § 174.25.

modification of the genome could have been achieved in the alternative using conventional breeding and/or induced mutagensis. As noted above, USDA has promoted this approach, and it seems reasonable that the EPA could follow that same path and decide not to regulate such products of gene editing even though the result is a new pesticidal activity. To this author's knowledge, EPA has not issued a statement directly addressing this question. However, an EPA PowerPoint presentation dated May 2018 and posted online does state: (1) the FIFRA exemption for pesticidal activity introduced through conventional breeding predates site-specific gene editing technologies like CRISPR; (2) "knockouts could still be considered as PIPs depending on claims made and intent of product (*e.g.*, disease resistance)"; and (3) "PIPs would need to be specifically exempted from FIFRA through rule-making in order to bypass regulation."[39]

The EOP's 2016 *National Strategy for Modernizing the Regulatory System for Biotechnology* states that the EPA has committed to clarifying its approach to pesticidal products derived from genome editing techniques in a manner "consistent with the principles for the regulation of biotechnology products articulated in the Coordinated Framework and the goals and objectives of the July 2015 EOP memorandum."

Under its current interpretation of its own regulatory jurisdiction EPA would not have a basis for asserting regulatory authority over gene-edited plants that have not been engineered to express a pesticide. However, there has reportedly been internal pressure at EPA to expand the agency's regulatory reach under the TSCA.[40] The NAS Report states that the Coordinated

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[39]Chris A. Wozniak, *Regulatory Avenues at US EPA for Products of Novel Breeding Technologies* (EPA Office of Pesticide Programs May 9, 2018), available at http://cropbioengineering.iastate.edu/wp-content/uploads/2018/06/2-Day2_Wozniak.pdf (last visited Jan. 3, 2019).

[40]Henry Miller and John Cohrssen, *Viewpoint: It's Time to Replace Our Fear-Based Genetic Engineering Regulations*, GENETIC LITERACY PROJECT (Oct. 17, 2018), available at https://geneticliteracyproject.org/2018/10/17/viewpoint-its-time-to-replace-our-fear-based-genetic-engineering-regulations/ (last visited Jan. 3, 2019).

Framework, as drafted in 1986, described the TSCA as a "back-stop" authority that could be applied to any biotechnology organism that did not fall under the jurisdiction of any other statute or agency.[41] However, I must point out that when this author read the Coordinated Framework as drafted in 1986, I did not see reference to the TSCA as a back-stop. The NAS Report also states that in 2001 the Executive Office of the President's Office of Science and Technology Policy and Council on Environmental Quality's biotechnology case studies concluded that EPA has authority under the TSCA over a variety of biotechnology organisms, including plants and animals, although this author was unable to access any document that would confirm this.[42] The NAS Report goes on to note that to date, EPA does not appear to have exercised its authority under TSCA in this way, and questions whether this regulatory restraint is due to insufficient resources or to the agency's interpretation of its own authority under the statute. The Report states that it "would be helpful if the federal government would make a policy determination as to whether EPA will serve this gap-filling role."

FDA. In January 2017, the FDA published a Request for Comments on questions related to use of genome editing in new plant varieties used for food for humans and animals.[43] In October 2018, FDA issued its *Plant and Animal Biotechnology Innovation Action Plan*, which provides an "overview of the key priorities the FDA will pursue to support innovation in plant and animal biotechnology and to advance the agency's public health mission."[44] The Plan summarizes FDA's efforts to respond to advances in biotechnology, and particularly points to

[41]NAS Report, *supra* note 2, at 95.
[42]*Id.*
[43]FDA, Genome Editing in New Plant Varieties Used for Foods; Request for Comments, 82 Fed. Reg. 6564 (Jan. 19, 2017).
[44]FDA, *Plant and Animal Biotechnology Innovation Action Plan* (Oct. 2018), available at https://www.fda.gov/downloads/Safety/Biotechnology/UCM624517.pdf (last visited Jan. 3, 2019) ("Human medical products such as human drugs, biologics, and medical devices are not within the scope of activities envisioned under this Action Plan.").

genome editing as a technology with huge potential in areas including food, agriculture, and health, but also potential risks.

The Action Plan identifies three areas of priority: (1) advancing public health by promoting and fostering innovation in animal and plant biotechnology; (2) strengthening public outreach and communication; and (3) increasing engagement with domestic and international partners.

Regarding the first priority, promoting innovation in animal and plant biotechnology, the Plan promotes a "flexible, risk-based approach . . . focusing on safety, effectiveness, and/or regulatory questions relevant to each product for its intended use," including, "when appropriate, updating and clarifying science-based policies to support innovation and ensure that [FDA] regulatory processes are efficient, predictable and proportionate to risk."

With respect to plant biotechnology, the plan states that the FDA intends to publish draft guidance for industry to explain FDA's current regulatory policy for human and animal foods produced through modern molecular plant breeding techniques. In addition, over the next two years, the FDA intends to "begin updating the existing procedures for voluntary premarket consultations with industry to reflect the FDA's 25 years of experience with foods derived from biotechnology plants and considering any additional issues related to genome editing of food crops."

The EU

The regulatory requirements for genetically modified non-human organisms in the European Union is rooted in the "GMO Directive."[45] The GMO Directive imposes substantial regulatory obligations on member states that cover any (1) deliberate release into the environment of a genetically modified organism (GMO) and (2) any introduction of a GMO product on the market within the Union. The Directive requires member states to evaluate GMO products for potential risks to the environment or human or animal health prior to release into the environment or marketing. GMO products are also subject to traceability, labelling, and monitoring obligations.

The GMO Directive emphasizes that the "precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it." As a practical matter, the Directive requires member states to impose regulatory requirements on GMO products, such as genetically modified crops, that are quite burdensome compared to the United States and much of the rest of the world. As a result of the more burdensome regulation, Europe has lagged far behind the U.S. and other nations in its adoption of genetically modified organisms in agriculture, and this has probably led to less research into agricultural biotechnology in Europe than would have been the case under a less stringent regulatory regime.

By its terms, the GMO Directive applies to the release and marketing of any GMO, which the Directive defines as any organism, other than a human being, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural

[45]Directive 2001/18/EC, available at http://curia.europa.eu/juris/document/document.jsf?docid=204387&mode=req&pageIndex=1&dir=&occ=first&part=1&text=&doclang=EN&cid=3205302 (last visited Jan. 3, 2019).

recombination. The Directive focuses on the technique used to produce the genetic modification, and provides a nonexclusive list of specific techniques that do result in a genetic modification for purposes of the Directive:

> (1) recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;
>
> (2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation; and
>
> (3) cell fusion (including protoplast fusion) or hybridization techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally."[46]

On the other hand, the GMO Directive specifically identifies several techniques that are not considered to result in genetic modification:

> (1) *in vitro* fertilization;
>
> (2) natural processes such as: conjugation, transduction, transformation; and
>
> (3) polyploidy induction.[47]

[46]Annex I A, part 1.

Finally, the Directive identifies certain techniques that are considered to result in genetic modification of an organism, but that are specifically exempted from regulation under the Directive:

> (1) mutagenesis, and
>
> (2) cell fusion (including protoplast fusion) of plant cells or organisms which can exchange genetic material through traditional breeding methods.[48]

These exemptions are intended to encompass techniques used for genetic modification that are not "natural," but that predate the modern tools of biotechnology, such as recombinant DNA technology. The justification for the exemption of these techniques is that they have a long track record and have not been found to create any particular risks to the environment or health. As a practical matter, the Directive has only covered the sorts of products that originally spurred the EU's adoption of the Directive, transgenic crops that include genetic material from another source organism and which it would not have been feasible to create using pre-biotechnology techniques.

The European Court of Justice Decision

In 2018, the European Court of Justice (ECJ) issued a decision (the ECJ Decision) that addresses the important question of how the GMO Directive is to be applied to genetically modified organisms produced using techniques that were presumably not considered when the

[47]Annex I A, part 2.
[48]GMO Directive, Article 3(1), read in conjunction with Annex I B.

Directive was put into effect in 2001.[49] More particularly, should new methods of mutagenesis, including mutagenesis by target-specific gene editing like CRISPR, and mutagenesis conducted *in vitro*, be exempt from the Directive pursuant to the "mutagenesis exemption" described above, or should they be subjected to the more stringent regulation applicable to the transgenic products specifically contemplated in the Directive?

The ECJ Decision arose out of an action brought against the French Prime Minister by a coalition of groups opposed to the use of GMOs in agriculture (the Applicants) seeking annulment of a French law that, pursuant to the GMO Directive, exempts organisms obtained by mutagenesis from the regulatory requirements applicable to GMOs. They also sought to compel the French government to reverse its decision to allow the cultivation and marketing of herbicide-tolerant rape varieties that were produced through mutagenesis, and to order the Prime Minister to impose a moratorium on herbicide-tolerant plant varieties obtained by mutagenesis.

The Applicants argued that at the time the Directive was drafted to include a mutagenesis exemption, the only mutagenesis techniques that were being used routinely were "conventional" techniques performed *in vivo* and involving ionizing radiation or exposing plants to chemical agents. "New mutagenesis techniques" involving *in vitro* random mutagenesis and directed mutagenesis were not under consideration when the drafters of the Directive created the exemption for mutagenesis. The Applicants argued that these new mutagenesis techniques had made it feasible to produce GMO products that, as a practical matter, could not have been made using conventional mutagenesis, such as ones resistant to nonspecific herbicides like glyphosate. The Applicants argued that the use of the herbicide-resistant seeds made possible by the new

[49]Case 528/16, available at http://curia.europa.eu/juris/document/document.jsf?docid=204387&mode=req&pageIndex=1&dir=&occ=first&part=1&text=&doclang=EN&cid=3205302 (last visited Jan. 3, 2019).

mutagenesis techniques pose a significant risk of harm to the environment and to human and animal health. They also expressed concern about the risk of unintentional effects, such as undesired or off-target mutations occurring in other parts of the genome.

To this author it appears that the Applicants' primary objection it is directed towards the use of herbicide-resistant seeds, not the techniques used to make them per se. The problem they have with gene editing and other new mutagenesis techniques seems to be that that these techniques are much more powerful than conventional techniques for crop improvement, and thus likely to result in a proliferation in Europe of herbicide-resistant crops and other forms of crop improvement that the Applicants find objectionable.

In its July 25, 2018, decision, the ECJ held that organisms modified by means of gene editing and other new mutagenesis techniques are GMOs for purposes of the Directive, and not subject to the mutagenesis exemption, which was found to only be available to organisms produced using conventional mutagenesis techniques. In arriving at its decision, the ECJ looked towards what it perceived to be the intent of the drafters of the Directive, in particular the specific statement in the Directive that it was drafted in consideration of the precautionary principle, and that the precautionary principle is to be used in interpreting the Directive's scope and effect.

The Court found in particular that the mutagenesis exemption was based on the long safety record of conventional mutagenesis techniques. In contrast, the Court found that the risks to the environment or human health associated with methods of directed mutagenesis involving the use of genetic engineering which have arisen after the GMO Directive was drafted have thus far not been established with certainty. "[I]n essence, the risks linked to the use of those new

techniques/methods of mutagenesis might prove to be similar to those which result from the production and release of a GMO through transgenesis."

The Court further found that that the direct modification of the genetic material of an organism through mutagenesis makes it possible to obtain the same effects as the introduction of a foreign gene into that organism, and that the development of those new techniques/methods makes it possible to produce genetically modified varieties at a rate and in quantities quite unlike those resulting from the application of conventional methods of random mutagenesis. "Whether released into the environment in large or small amounts for experimental purposes or as commercial products, [these organisms] may reproduce in the environment and cross national frontiers, thereby affecting other Member States. The effects of such releases on the environment may be irreversible."

The upshot of the decision is that, so long as it remains in place, member states of the European Union will be required to regulate products of gene editing and other new mutagenesis techniques in the same manner as conventional GMOs. As a practical matter, this would appear to constitute a near *de facto* ban on cultivating gene-edited crops in Europe, as most member states have essentially prohibited GMOs.[50] Only one genetically modified food crop, an insect-resistant corn, has ever been approved in the EU.[51] Cornell's Alliance for Science aptly points out that, "Europe now faces the bizarre situation of subjecting new plant varieties produced by

[50]Joan Conrow, *US Ag Secretary Rejects Europe's Gene Editing Ruling*, CORNELL ALLIANCE FOR SCIENCE (July 31, 2018), available at https://allianceforscience.cornell.edu/blog/2018/07/us-ag-secretary-rejects-europes-gene-editing-ruling/ (last visited Jan. 3, 2019) (Dr. Sarah Schmidt of the Institute for Molecular Physiology at Heinrich-Heine-Universität Düsseldorf said it delivered "the deathblow for plant biotech in Europe.").

[51]Mark Lynas, *Scientific Community Defeated by Green Groups in European Court Ruling on Gene Edited Crops*, CORNELL ALLIANCE FOR SCIENCE (July 26, 2018), available at https://allianceforscience.cornell.edu/blog/2018/07/scientific-community-defeated-green-groups-european-court-ruling-gene-edited-crops /(last visited Jan. 3, 2019).

precise gene editing to zealous and expensive regulation, while allowing hit-and-miss radiation mutagenesis to continue to get a free pass."[52]

The ECJ Decision was met with shock and dismay by proponents of biotechnology in the European Union and abroad.[53] The European Seed Association responded by declaring the ruling "a watershed moment for the EU's agri-food chain." ESA Secretary General Garlich von Essen noted: "It is now likely that much of the potential of these innovative methods will be lost for Europe—with significant negative economic and environmental consequences. That strikes a serious blow to European agriculture and plant science."[54] As von Essen observed, "while other parts of the world go ahead with these innovations without unnecessary overregulation, Europe's breeders and farmers will once again lose out, without a chance to explore the huge potential and benefits of these plant breeding innovations in practice."[55]

In the UK, a group of scientists and industry leaders responded with an open letter to the Secretary of State for Environment, Food, and Rural Affairs calling on the UK government to provide clarity on the future of gene-edited crops in that country, particularly in view of Brexit and the uncertain future relationship between the UK in the EU.[56]

The UK letter warns that the ECJ's ruling has profound implications for:

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[52]*Id.*

[53]*Id.*

[54]European Seed Association, *A Bleak Future for Agricultural Innovation in the EU*, EUROSEEDS.EU (July 25, 2018), available at https://www.euroseeds.eu/bleak-future-agricultural-innovation-eu (last visited Jan. 3, 2019).

[55]*Id.*

[56]*See* letter from Professor Dale Sanders *et al*. to The Rt Hon Michael Gove, MP, Secretary of State for Environment, Food and Rural Affairs regarding organisms obtained by mutagenesis (Sept. 13, 2018), available at http://www.cpm-magazine.co.uk/wp-content/uploads/2018/09/180903-Michael-Gove-letter.FINAL_.pdf (last visited Jan. 3, 2019).

> (1) UK researchers who are currently carrying out public-funded work into gene-edited crops in research institutes and universities that is set to deliver innovative solutions to tackle world hunger and crop adaption to climate change;
>
> (2) UK plant breeders who will be obligated to segregate material, but will have no means of testing material they wish to introduce into breeding lines to establish whether it originates from an organism obtained by mutagenesis;
>
> (3) UK farmers who are tasked with producing food sustainably at world-market prices, under challenging and volatile circumstances, including changes in the support framework, but do not have access to the full range of innovative tools available to other farmers around the world;
>
> (4) The UK agri-food industry that has already seen investment in R&D into European agriculture by large multinational companies fall from around 33 percent of global total 30 years ago to less than 8 percent, purely as a result of an unscientific approach taken at an EU level to the precautionary principle;
>
> (5) UK consumers, 70 percent of whom support the use of genome editing in plants to make crops more nutritious as a way of supplementing poor diets; and
>
> (6) International trade, where there is a serious risk that differences in regulatory status of gene-edited products will lead to major disruption, complicated by an inability to distinguish between gene-edited and conventionally bred material.[57]

The German Bioeconomy Council, a panel of 17 researchers who advise the German Federal Government, responded to the ECJ Decision by calling for new EU legislation governing

[57] *Id.*

crops created by plant-breeding technologies such as CRISPR.[58] In a statement, the Council noted, "[i]n its current form, EU genetic engineering legislation cannot do justice to the opportunities and challenges of the technologies. We need an amendment to bring it in line with advances in the field. It is important to have a regulation that distinguishes between mutations and gene transfers and provides for risk-oriented approval and release procedures." In addition to calling for legislation that is suited to the different applications of new technologies, the Council also argued that mandatory product labeling is not practical since modifications cannot always be scientifically or technically detected or proven in the end product.

In its statement, the Council recommends that Germany adopt legislation "that is more suited to the many different applications of the new technologies, from simple mutations right through to complex genome editing, and their different risk assessments; for example, graduated licensing and approval procedures for different classes of risk." The Council also suggests that "[i]n view of international trade and global supply chains, mandatory product labelling is not sensible, since modifications cannot always be scientifically or technically detected or proven. In order to promote consumer information and transparency, the infrastructure for voluntary certification (*e.g.*, 'GMO-free') should be strengthened." The Council also encourages an intensification of international exchange and collaboration in order to guarantee greater transparency and regulatory harmonization.

On November 13, 2018, the EU Group of Chief Scientific Advisors responded to the ECJ Decision with a document entitled *A Scientific Perspective on the Regulatory Status of Products*

[58]Press Release, Bioeconomy Council of the Federal German Government, Genome Editing: Germany's Bioeconomy Council Calls for New EU Legislation (Sept. 17, 2018), available at http://biooekonomierat.de/fileadmin/Pressemitteilungen/BO__R_GenomeEditing_PM_eng_final_2.pdf (last visited Jan. 3, 2019).

Derived from Gene Editing and the Implications for the GMO Directive (the "Scientific Perspective").[59] The Scientific Perspective come to the conclusion:

> in view of the [ECJ]'s ruling, it becomes evident that new scientific knowledge and recent technical developments have made the GMO Directive no longer fit for purpose. Moreover, the GMO Directive gives rise to more general problems, in particular with regard to the definition of GMOs in the context of naturally occurring mutations, safety considerations, as well as detection and identification.

The Scientific Perspective points out that when the GMO Directive was adopted in 2001, gene editing had not yet been applied to agricultural organisms. It goes on to find that gene editing techniques are more precise and produce fewer unintended effects than random mutagenesis techniques, that the end product is better characterized, and that unintended effects will occur less frequently. Consequently, the products of gene editing are potentially safer than the products of random mutagenesis. In addition, gene editing techniques result in fewer intermediate and unwanted varieties compared to random mutagenesis techniques.

The Scientific Perspective points out that the GMO Directive has often been interpreted as being focused solely on production technique rather than the characteristics of the resulting product, whereas from a scientific perspective the characteristics of the product are more relevant than the technique used to generate them. It further points out that the Applicants' concern about potential environmental and safety risks of herbicide-resistant seed varieties is not addressed by subjecting organisms produced by directed mutagenesis to the obligations of the GMO Directive

[59]Scientific Perspective, *supra* note 9.

because herbicide-resistant seeds could in principle be produced using random mutagenesis or other conventional breeding methods.

The Scientific Perspective goes on to explain that it will often be impossible to detect products of gene editing because they will be indistinguishable from mutations that have occurred spontaneously or are the product of conventional breeding technology. The EU Scientific Advisors report that a document is currently under preparation by the European Network of GMO Laboratories, together with the European Commission's Joint Research Center, which will look in more detail at the issues related to detection, identification, and quantification.

The Scientific Perspective observes that "meeting the obligations of the GMO Directive implies cost- and labor-intensive pre-market evaluations and a long duration of the approval process, which are difficult and onerous to bear, particular by small and medium enterprises," and that "this may diminish incentives for investment, negatively affect research and innovation in this field, and limit the commercialization of gene edited crops." The Scientific Advisors specifically point to the concern that countries in the developing world exporting food and feed to the EU might not benefit from gene-edited crops if they follow the EU authorization practice, as some of them currently do, and that gene editing has the potential to contribute to food security, which is particularly relevant given the growing world population and climate change.

In short, the Scientific Perspective finds a need for improving the EU's GMO legislation to render it "clear, evidence-based, implementable, proportionate and flexible enough to cope with future advances in science and technology in this area." The Scientific Advisors recommend a revision to the existing GMO Directive to "reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification."

U.S. Secretary of Agriculture Sonny Perdue responded quickly to the ECJ ruling with a statement calling the decision a setback to scientific innovation that creates unnecessary regulatory barriers and unjustifiably stigmatizes new technologies, by finding newer genome editing methods to be within the scope of the European Union's "regressive and outdated regulations governing genetically modified organisms."[60] His statement encourages the EU to seek input from the scientific and agricultural communities, as well as its trading partners, in determining the appropriate implementation of the ruling. "The global regulatory treatment of genome-edited agricultural products has strategic innovation and trade implications for U.S. agriculture. . . . In light of the [ECJ] ruling, USDA will re-double its efforts to work with partners globally towards science- and risk-based regulatory approaches."

Canada

The Canadian regulatory approach has, like that in the U.S., focused on the characteristics of the product rather than the technique used to make the product. Canada requires a pre-market safety assessment for agricultural biotechnology products, including products of gene editing, only if the product expresses a new trait and could therefore pose any risk. On the other hand, a product of gene editing that does not express a novel trait does not require a pre-market safety assessment. In a recent presentation, the Director of the Canadian Food Inspection Agency, Christine Tibelius, noted that since the same trait can be introduced into a plant by any of a variety of processes, including breeding, random mutagenesis, targeted

[60]Press Release, USDA, Secretary Perdue Statement on ECJ Ruling on Genome Editing (July 27 , 2018), available at https://www.usda.gov/media/press-releases/2018/07/27/secretary-perdue-statement-ecj-ruling-genome-editing (last visited January 3, 2019).

mutagenesis, genetic deletion, or through transgenics, it is the risk of the trait that is to be assessed under the Canadian system, irrespective of the technique used.[61]

Japan

Japan has not embraced agricultural biotechnology, and there are reportedly no GMO crops currently being grown commercially in Japan.[62] According to a survey of people with food industry experience conducted by the Environmental Ministry's Food Safety Commission of Japan, more than 30 percent of respondents said that even if a genetically modified crop had been evaluated by the government for safety, they would still "feel anxious" about it.[63]

This has not deterred Japan from addressing the regulation of agricultural products of gene editing. On August 20, 2018, Japan's Ministry of Environment (MOE) held its second technical meeting to discuss the handling of genome editing technology under the Cartagena Protocol on Biosafety.[64] The committee primarily focused on two issues: (1) the scope of genome editing technologies which could potentially be regulated under the "Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms" known as the Cartagena Protocol on Biosafety (the Cartagena Protocol), and (2) the handling of technologies which would be out of scope of the Protocol (as the result of discussion of the first issue).

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[61]Christine Tibelius, Director, Canadian Food Inspection Agency, *Canadian Regulatory Aspects of Gene Editing Technologies*, OECD Conference on Genome Editing (June 29, 2018), available at https://www.slideshare.net/OECD_ENV/canadian-regulatory-aspects-of-gene-editing-technologies-christine-tibelius(last visited Jan. 3, 2019).

[62]Kazuhiro Igarashi and Kosuke Hatta, *Env. Ministry Committee Proposes Deregulating Some Genetically Edited Organisms*, MAINICHI (Aug. 21, 2018), available at https://mainichi.jp/english/articles/20180821/p2a/00m/0na/033000c (last visited Jan. 3, 2019).

[63]*Id.*

[64]USDA Foreign Agricultural Service, *Japan: Japan Holds Second Meeting to Discuss Genome Editing Technology* (Aug. 20, 2018), available at https://www.fas.usda.gov/data/japan-japan-holds-second-meeting-discuss-genome-editing-technology (last visited Jan. 3, 2019).

The committee distinguished between genome editing that adds an exogenous gene to the genetic code of an organism, and editing that eliminates or disables sections of the organism's genome but inserts nothing new. Organisms produced using the former method, the committee concluded, could impact the environment by interbreeding with preexisting species and creating hybrids, and therefore required regulation under legislation based on the Cartagena Protocol.[65]

On the other hand, the committee concluded that products of genome editing technology that do not contain "foreign nucleic acids and/or its copies" will not be categorized as genetically engineered under the Cartagena Protocol. Similarly, the modification of the genome and the introduction of genes which could occur naturally and/or through conventional cross breeding will not be regulated as GE either (*e.g*., self-cloning and natural occurrence). [66] The committee also judged that even organisms created by adding genes do not require regulation as long as the alteration does not become permanent, *i.e*., null segregants.[67]

WTO statement

On October 30, 2018, a World Trade Organization (WTO) Committee issued a statement supporting policies that facilitate agricultural innovation, including genome editing.[68] As of November 2, twelve nations had signed on to the statement, including Australia, Brazil, Canada, Colombia, the Dominican Republic, Guatemala, Honduras, Jordan, Paraguay, the United States, Uruguay, Vietnam, and the Secretariat of the Economic Community of West African States.[69]

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[65]Igarashi and Hatta, *supra* note 62.
[66]USDA Foreign Agricultural Service, *supra* note 64.
[67]Igarashi and Hatta, supra note 62.
[68]WORLD TRADE ORGANIZATION (WTO) COMMITTEE ON SANITARY AND PHYTOSANITARY MEASURES, INTERNATIONAL STATEMENT ON AGRICULTURAL APPLICATIONS OF PRECISION BIOTECHNOLOGY (Oct. 30, 2018).
[69]Press Release, USDA, WTO Members Support Policy Approaches to Enable Innovation in Agriculture (Nov. 2, 2018), available at https://www.usda.gov/media/press-releases/2018/11/02/wto-members-support-policy-approaches-enable-innovation-agriculture (last visited January 3, 2019).

The primary objective of the statement is to coordinate efforts ensuring that the regulatory approaches for agricultural products produced using precision biotechnology techniques, including gene editing, are scientifically based and internationally harmonized, in order to prevent regulatory asymmetries and, in turn, potential trade disruption. The signatory nations agree that precision biotechnology techniques, as a whole, constitute an essential tool for agricultural innovation, providing farmers with access to products that increase productivity while preserving environmental sustainability, and recognize the important role that gene editing and other forms of precision biotechnology could play in addressing global environmental challenges, pest and disease pressures, food insecurity, and changes in consumer preferences.

The statement concludes that organisms produced using gene editing and other forms of precision biotechnology may in some cases generate organisms with characteristics similar to those obtainable through conventional breeding, while in other cases, the organisms generated may have characteristics similar to those introduced into organisms using recombinant DNA technologies. In either case, the statement finds that the food, animal, and environmental safety of such products can be adequately addressed by existing regulatory frameworks for agricultural products and existing safety standards based on the characteristics of the product or organism.

The statement warns that differing domestic regulatory approaches for products derived from precision biotechnology may result not only in international asynchronicity in approvals, but also in asymmetry in regulatory approaches, and may create potential trade issues that could impede innovation. It urges governments to exercise due consideration in assessing the products of agricultural biotechnology, in order to avoid arbitrary and unjustifiable distinctions between end products derived from precision biotechnology and similar end products obtained through other production methods. It also encourages government cooperation to minimize unnecessary

barriers to trade related to the regulatory oversight of products of precision biotechnology, including the exploration of opportunities for regulatory and policy alignment.

CONCLUSION

In short, CRISPR and other advances in gene editing are destined to bring transformative changes to agriculture around the world. The U.S. and most other nations are embracing the technology, and appear open to regulatory reform that focuses on the nature of the product and reasonably foreseeable risk, while for the time being, the ECJ's decision to subject agricultural products of gene editing to burdensome regulation will no doubt impede its development in Europe.

The European decision is unfortunate in many respects.[70] To name one, it has been pointed out that the decision will likely have serious implications for Africa, where CRISPR is currently being used to develop disease-resistant varieties of important food crops such as cassava.[71] According to the European Commission, Africa is the EU's single largest trading partner, with Europe importing nearly $16 billion in agricultural and food products from Africa in 2017.[72] With a *de facto* moratorium on these products in Europe, African farmers hoping to sell to European markets might not be able to take advantage of improvements obtainable through gene editing. For these and other reasons, it is to be hoped that the EU takes the advice of its own Chief Scientific Advisors and finds a way to reverse the anti-technology effect of the Court of Justice's decision.

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[70]Joan Conrow, *US Ag Secretary Rejects Europe's Gene Editing Ruling*, CORNELL ALLIANCE FOR SCIENCE (July 31, 2018), available at https://allianceforscience.cornell.edu/blog/2018/07/us-ag-secretary-rejects-europes-gene-editing-ruling/

[71]Eric Niiler, *European Ruling Could Slow Africa's Push for CRISPR Crops*, WIRED (July 25, 2018), available at https://www.wired.com/story/european-ruling-could-slow-africas-push-for-crispr-crops/ (last visited Jan. 3, 2019).

[72]*Id.*