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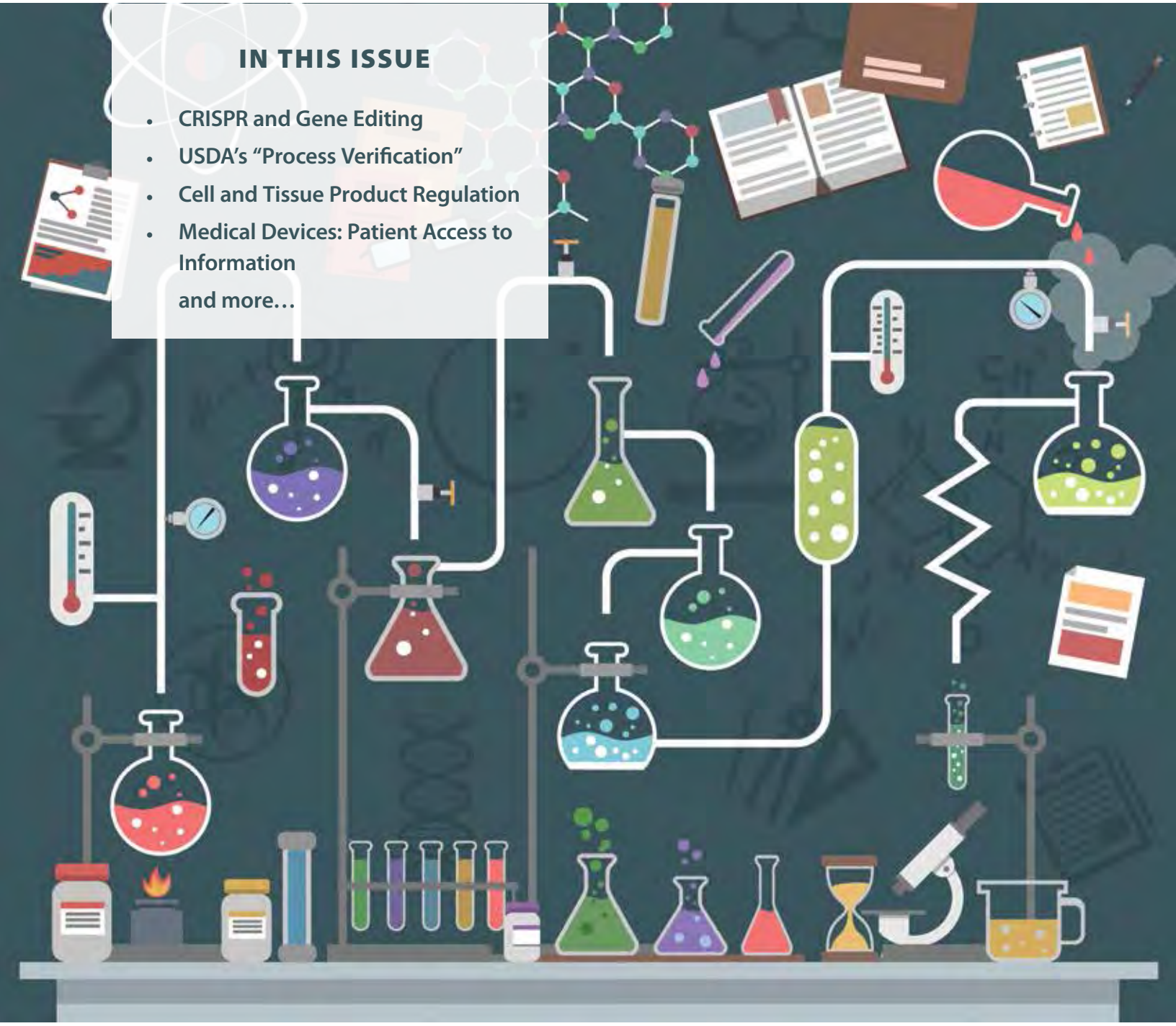

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Ready or Not, CRISPR and Gene Editing Have Arrived and Are Here to Stay

by Jay W. Cormier and Ricardo Carvajal

Ever since 1953, when James Watson and Francis Crick built on the earlier work of Rosalind Franklin and Maurice Wilkins to define the structure of DNA, molecular biologists have been learning how to manipulate that basic building block of life. Nearly fifty years later, in 1999, the human genome was first fully sequenced, and within ten more years scientists had started identifying ways to make specific small changes to the genome. In the mid-2000s, scientists spoke of zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and meganucleases, but those technologies were expensive and difficult to work with in the lab.

Over the course of roughly the last year, gene editing has gone from being a topic limited to scientific conferences to being featured in the *New York Times* and on the cover of *TIME* magazine. Most of the attention has been due to a molecular tool with an opaque name but simple acronym: clustered, regularly interspaced, short palindromic repeat (CRISPR)

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technology. Despite all the attention that has come to CRISPR and gene editing in general, many legal questions linger; it is not immediately clear how the U.S. Food and Drug Administration (FDA) will approach the regulation of various applications of this powerful technology.

In this article, we attempt to provide a common understanding about gene editing and CRISPR. We then discuss potential applications of the technology as well as regulatory issues in the FDA and U.S. Department of Agriculture (USDA) arenas.

Gene Editing Versus Genetic Engineering and GMOs—Tomato, Tomahto?

The lexicon of advanced genetics is expanding, and can be confusing. Genetic engineering is the process of purposefully introducing changes to a genome via any number of various molecular biology tools. This can encompass small single nucleotide changes to a genome as well as transgenesis—the introduction of DNA sequences normally found in one species into a second species where those sequences are not normally found. Whether small or larger genomic changes are made, before the emergence of "gene editing" all such changes require use of specific genetic tools to combine various pieces of DNA together in test tubes prior to engineering of a given genome. The resulting DNA sequences are then inserted into an organism's genome when a cell divides and the chromosomes of the organism go through a process of exchanging, or recombining, strands of DNA between chromosomes. Until the last ten years or so, this recombinant DNA (rDNA) technology was the only realistic way to engineer an organism's DNA.[1] Using rDNA technology, a genomic change can be made in a specific way or a new rDNA sequence can be inserted into the genome randomly.

Although not scientifically synonymous, public understanding of genetic modification is that the term is just another way of saying genetically engineered. To be clear, there are any number of ways to "modify" an organism's genome without specifically engineering it; for example, random mutagenesis uses mutagens to introduce a large number of random genomic changes in search of new and desired traits. Selective breeding, which has been the foundation for all domestication of livestock and plants for millennia, is much the same—offspring with desired traits (e.g., drought resistant crops or animals that are more docile when interacting with humans) are purposely chosen to be overrepresented in following generations, even though the number of genomic changes enhanced by this method is significantly more than just the specific genetic changes that give rise to the desired trait.[2] While science suggests, then, that "genetically modified" should be a much larger set of man-made genetic changes to a genome than "genetically engineered" would include, genetically modified organisms (GMOs) has come to be limited to only those organisms that have been genetically engineered.

Scientifically speaking, the term "gene editing" refers to the intentional alteration of an organism's genome while employing one of a number of various enzymes (called nucleases), the function of which is to make specifically-targeted changes to the genome. These enzymes include ZFNs, TALENs, and the CRISPR system. In the popular press, gene editing is presented as a process that, "with the precision we have come to expect from the search-and-replace function of a word processor," can selectively change sequences of the genome to, for example, correct a genetic error that is known to cause diseases such as Huntington's disease and sickle-cell anemia.[3] As will be discussed in more detail below, however, CRISPR can, theoretically, be used to insert large sequences of DNA—specifically rDNA—just as earlier genetic engineering techniques have for decades. Thus, depending on the application, the distinction between gene editing and genetic engineering may really be a distinction without a difference.

What is CRISPR, How Does It Work, and Why Is It Such a Big Deal?

CRISPR technology is a molecular tool that was created by making adjustments to a bacterial immune system. It turns out that adaptive immunity—changing one's defense against pathogens in response to exposure to pathogens—is not something reserved for us multi-cellular organisms. Even single-celled organisms have developed this skill, however rudimentary. While the bacterial adaptive immune system is clearly less sophisticated than the mammalian immune system that uses a complex multi-cellular system to identify, target, eradicate, and prepare for subsequent infection from any one of a vast number of potential pathogens, the bacterial immune system is no less clever. The bacterial genome contains a number of repeating DNA sequences that are used by the bacteria to determine whether a virus is infecting the cell, and, if so, to use a specific enzyme that targets the viral DNA to cut the DNA into pieces. Cutting the invading viral DNA serves two purposes. First, the invading virus is no longer infectious when it has been cut into pieces too small to be a problem for the bacteria. Second, and more interestingly, the pieces of DNA are added to the

repeating pieces of DNA in the bacterial genome to help the bacteria identify the same virus again the next time the virus attempts to infect the bacteria.

Thus, the CRISPR system is comprised of two parts: an RNA targeting sequence (made from transcribing the repeating DNA sequences into RNA strands); and a nuclease—referred to as a CRISPR-associated (Cas) nuclease—that complexes with the RNA targeting sequence and cuts DNA sequences that match that of the RNA targeting sequence.

At first blush, one might be curious at all the fuss. Traditional rDNA technology uses engineered nucleotide sequences to selectively target sequences in an organism's genome to make specific intentional changes, whether insertions, deletions, or changes in one base pair or an entire gene. The CRISPR/Cas system is fundamentally the same. Indeed, if each method is carefully executed, a scientist could produce two organisms with identical changes using each of traditional rDNA technology and the CRISPR/Cas system and no other scientist would be able to determine which one was created using which technology.

The significant insight roughly four years ago was that if one could specifically engineer the RNA target sequence with an appropriate Cas nuclease, then one could, theoretically, target any DNA sequence and use target RNA complexes to use a cell's innate system for fixing the CRISPR-introduced cuts to introduce, remove, or change sequences in the host genome. In early 2013, scientists demonstrated use of the CRISPR-Cas9 complex to selectively edit the genome of human cell lines.[4] The CRISPR era of genome editing was born.

The exciting (and, frankly, frightening—but more on that below) unique potential of the CRISPR/Cas system takes us away from molecular biology and into economics. Directing changes in a genome using traditional rDNA technology requires highly skilled personnel and is extremely inefficient. It can take years to design and build the rDNA constructs, to inject them into cells and hope that the cell's chromosomes recombine at just the right places to allow the rDNA construct to recombine and integrate into the organism's genome. ZFNs and TALENs offered a shortcut, significantly increasing the yield by directing genomic changes rather than relying on the randomness of chromosomal recombination, but are tricky to use even in the most skilled of technical hands. These nucleases were a significant step forward for the laboratories that had the personnel who could successfully use them. CRISPR/Cas, however, offers the same shortcut as the other nucleases, but the system is remarkably robust.

The impact of CRISPR/Cas has been compared to that of the DNA polymerase chain reaction (PCR) that is used to amplify specific pieces of DNA. When PCR was first discovered it was a tool used by graduate school departments but now is often a part of basic high school biology classes. CRISPR/Cas is cheap to use (already you can order your own CRISPR/Cas kit for as little as $130[5]) and is easy enough to use that labs all over the world are already using the technology. It is only a matter of time before high school students will be editing genomes as part of their regular curricula using CRISPR/Cas. In a word, CRISPR/Cas is transformative.

Potential Applications—The Good, the Bad, and the Ugly

Because it is possible to completely engineer the entire sequence of the RNA targeting sequence used by the CRISPR/Cas system, the only limit to what edits can be made to which organism is the imagination of the scientist designing the experiment. The potential applications, then, are similarly limitless. During the five weeks from June 1 to July 7, 2016, over 300 scientific journal articles were published on actual or potential uses for the CRISPR system.[6] Those papers alone included reports of using CRISPR to edit the zebrafish genome in order to learn about the pathophysiology of fatal human kidney diseases,[7] production of pigs with multiple genetic edits with an aim to produce organs for xenotransplantation into humans,[8] to study how the Zika and Dengue viruses infect human cells,[9] to develop new methodologies to study potential breast cancer treatments,[10] and to learn how butterfly wing patterns are created.[11]

Due to the practically limitless possible applications of the technology, the CRISPR/Cas system raises a number of unsurprising issues. Soon, if it has not already begun, researchers at the Francis Crick Institute in London will become the first to edit the genomes of live, viable human embryos.[12] The edited embryos are not permitted to survive more than fourteen days; they will not be implanted and gestated to term. The scientists will be limiting their research to studying early human embryo development in order to gain insight into human infertility. But, there is no scientific reason why another set of scientists could not make entirely different edits and implant those embryos into women who are willing to pay for their children to be free of a specific inherited disease or to have a specific desired trait. The "threat" of designer babies and the ability for the resulting genes to be passed on to future generations has been of concern since the advent of rDNA techniques, but technical hurdles have

prevented scientists from going down this path. CRISPR/Cas likely presents the first realistic tool that would open the world to the possibility of successful editing of the heritable human genome.

Beyond engineering a human super-race and the eugenic overtones that presents, gene editing, courtesy of the ease of use and access to CRISPR/Cas technology, has been listed by the U.S. Department of Defense as a serious threat to national security. Each year, the Director of National Intelligence issues a Worldwide Threat Assessment for the U.S. Congress. In the 2016 version of that document, Director James R. Clapper discusses the most significant threats to national security, including, among others, cyber threats, terrorism, space and "counterspace," organized crime, and threats to natural resources.[13] In the category of Weapons of Mass Destruction and Proliferation, the Director lists six threat areas. In addition to the usual WMD threats of North Korea, China, Russia, Syria/Iraq (read ISIS), and Iran, the Director of National Intelligence lists "Genome Editing."[14] There, the document reads:

> Research in genome editing conducted by countries with different regulatory or ethical standards than those of Western countries probably increases the risk of the creation of potentially harmful biological agents or products. Given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications.[15]

The ethical issues regarding the appropriate (and inappropriate) use of CRISPR/Cas technology require such international coordination that the National Academy of Sciences, together with Chinese Academy of Sciences and the Royal Society of the United Kingdom, formed a Human Gene-Editing Initiative and held an International Summit on Gene Editing in Washington, D.C. in December 2015.[16] Subsequent meetings will be held before the group issues a final study report, expected later this year.[17]

The National Intelligence Director's statement, above, implicitly assumes a robust regulatory environment in, among other countries, the United States. At this point, it should come as no surprise that applications of CRISPR/Cas technology that potentially implicate FDA and/or USDA regulation are diverse. Just a few potential examples are listed below, organized by categories of applications.

- **Human Health**
  - Direct treatment of human disease in the human body[18]
  - Edit the genome of a patient's cells outside the body for subsequent reintroduction to the patient
  - Render pigs free of porcine retro viruses that could present risks when organs from those pigs are used for human xenotransplantation[19]
- **Food / Agriculture**
  - Confer health benefits to livestock, such as disease resistance
  - Increase agricultural value of live stock, such as cattle without horns
  - Increase agricultural value of produce[20]
- **Tobacco**
  - Produce tobacco plants that are resistant to disease or confer different health, organoleptic, or nicotine properties[21]

Regulatory Framework

Due to the differences in the statutes that grant FDA and USDA jurisdiction over various products, the regulatory framework for each is dramatically different.

A. FDA

Similar to other new technologies, and consistent with the Federal Food, Drug, and Cosmetic Act (FDCA), FDA's approach toward regulation of CRISPR/Cas technology will be based on the intended use of the technology. The FDCA defines "food," "food additive," "drug," and "tobacco" and the Public Health Service Act (PHS Act) defines "biological product" in terms of the use or intended use of the product.[22] Because FDA does not regulate based on the process used to generate the product, but rather based on intended use, the regulatory framework for CRISPR/Cas-derived products should be similar to those same products made via other processes.

Human Health Products

Were a company to seek approval of use of CRISPR/Cas directly administered to a patient, FDA would likely conclude that the targeting sequence/nuclease complex is a biological product subject to regulation in FDA's Center for Biologics Evaluation and Research (CBER). Marketing authorization would depend on the company demonstrating that the specific CRISPR/Cas complex can be reliably and consistently manufactured, is safe to use, and has its intended effect on the human patient. While efficacy will be similar to other biological products, the concept of product safety and quality manufacturing would be issues of first impression to FDA; CBER has not approved any gene

editing product as of this writing.

Ultimately, CBER would need to be confident that the CRISPR/Cas system chosen was specific enough that no untoward off-target effects would be observed. Because the technology would be new to CBER, we expect that CBER would take a very conservative approach toward the first approval of a human biological product that is a nucleic acid-nuclease complex intended to permanently change the phenotype of the target tissue. FDA would also need to consider the probability of off-target effects of the CRISPR/Cas system, even if the scientific literature states that this probability is low. As with all new technologies, we expect FDA to take a more precautionary approach until the agency is more comfortable with these products.

Were the CRISPR/Cas complex used to edit the genome of patient cells that have been removed from the body and used prior to re-implantation of the cells, the company seeking approval would have many of the same delays in approval, as above. In this case, however, the safety and off-target effects analysis is somewhat shortened, as the only human tissue that is exposed to the CRISPR/Cas complex are those cells that are isolated from the patient.

Animal Products, Including Those Used to Treat Human Disease

With respect to production of animals (whether livestock or pets or animals used to manufacture products used to treat human disease) using CRISPR/Cas technology, FDA would be expected to regulate these products similar to how FDA has regulated genetically engineered animals. In 2009, FDA's Center for Veterinary Medicine (CVM) issued a guidance document detailing its regulatory paradigm for genetically engineered animals.[23] That guidance document states, among other things, that FDA is regulating the rDNA construct used to engineer the animals as a new animal drug because it is intended to alter the structure or function of the animal and therefore meets the statutory definition of an animal drug.[24]

Although CVM's guidance only applies to products produced using traditional rDNA technology, we expect that CVM would approach CRISPR/Cas-generated animals similarly. Importantly, CVM has taken the position in that guidance document that because every cell of the animal contains an article that alters the structure or function of the animal, CVM asserts jurisdiction over the animal. Accordingly, CVM asks sponsors to keep records regarding the shipping and disposition of every genetically engineered animal. Furthermore, because the rDNA construct present in the genome of the original founder animal is inherited by the founder's offspring, CVM asserts jurisdiction over all subsequent generations of animals.

While these novel jurisdictional arguments are limited by guidance to genetically engineered animals, they are based on an agency interpretation of the statutory definition of a drug, which applies to both human and animal drugs. Thus, this same line of reasoning could, theoretically, apply to CRISPR/Cas editing of the human genome. We think it is highly unlikely that FDA would actually exercise jurisdiction over a human in the same way it does over an animal, but it presents an odd hypothetical reminiscent of law school exams.

Food Products

Because food derived from genetically engineered plants as a class does not present risks that differ from those presented by food derived through conventional breeding, FDA has implemented a voluntary consultation process for the introduction of such food into the human food supply. In any given case, FDA can choose to require premarket review and approval if the use of the food ingredient in question is not generally

recognized as safe (GRAS), and is therefore subject to regulation as a food additive. With respect to labeling, FDA has not required food derived from genetically engineered plants to be labeled as such, absent any material differences between such food and its conventional counterpart. There is no reason to expect that FDA will adopt a different approach to the oversight of gene-edited plants. Whether food derived from such plants will find greater market acceptance than food derived from genetically engineered plants remains to be seen. As this article was going to press, there was federal legislation under consideration in Congress that would authorize USDA to establish a national mandatory standard governing disclosure that a food is "bioengineered." USDA has indicated that any such standard would apply to plants that are gene-edited to yield traits that cannot be created through conventional breeding.

Tobacco

Because of the novelty of both gene editing and the regulatory framework for tobacco, it is unclear how FDA's Center for Tobacco Products (CTP) would approach the use of gene-edited tobacco in the manufacture of tobacco products. FDA has asserted jurisdiction over a broad range of tobacco products, and has moved to exercise tight control over the introduction of new products into the marketplace. To the extent that a genomic change wrought through gene editing results in a change in any constituent (including a smoke constituent) of a tobacco product, that change could render the product a "new" product that may require premarket review and approval. Due to FDA's overarching concern regarding the public health impact of tobacco products, we expect that FDA would lean in favor of premarket review of genomic changes to the tobacco plant, but a comprehensive analysis of that issue is beyond the scope of this article.

B. USDA

USDA's authority over genetically engineered crops derives from the Plant Protection Act (PPA). That statute gives USDA authority to prevent importation and dissemination of any "plant pest" (i.e., any article "that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product") or "noxious weed" (i.e., "any plant or plant product that can directly or indirectly injure or cause damage to crops . . . livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment").[25] USDA has concluded that certain CRISPR/Cas-edited plants are not subject to regulation under the PPA as plant pests when they do not contain any introduced genetic material (e.g., if the edit is limited to a deletion), and there is no reason to believe that they are plant pests. Further, such plants are not subject to regulation as noxious weeds when they are not listed as such, and when there is no reason to believe that the CRISPR/Cas phenotype would exhibit increased weediness.[26] Thus, the use of gene editing tools, including ZFNs, TALENs, and CRISPR/Cas to make small changes to a plant's genome without introducing DNA into the genome could make it less likely that the resulting plants would be subject to regulation as plant pests or noxious weeds.

C. The Coordinated Framework

In 1986, the Office of Science Technology Policy (OSTP), part of the Executive Office of the President (EOP), issued a statement that outlined a comprehensive federal regulatory policy for ensuring the safety of biotechnology products.[27] The statement, referred to as the Coordinated Framework for the Regulation of Biotechnology, sought to achieve a balance between regulation adequate to ensure the protection of health and the environment while maintaining sufficient regulatory flexibility to avoid impeding innovation. Under the Coordinated Framework, federal agencies would seek to first regulate biotechnology under existing statutes before seeking additional authority from Congress. The overarching regulatory approach was that the federal government would regulate the products of biotechnology, not the process by which those products were made.

On July 2, 2015, the EOP issued a memorandum directing the three agencies with primary responsibility for regulating the products of biotechnology—FDA, USDA, and the U.S. Environmental Protection Agency—to update the Coordinated Framework to ensure that the Framework was modernized and prepared for future biotechnological advancements.[28] The objectives of the update to the Coordinated Framework include, among other things, "[c]larifying the mechanism and timeline for regularly reviewing, and updating as appropriate, the [Coordinated Framework] to minimize delays, support innovation, protect health and the environment, and promote the public trust in the regulatory systems for biotechnology products."[29]

The update to the Coordinated Framework is underway. When the update will be completed is not definitively known, though OSTP is pushing for release of the update prior to the change of administration this coming January.

Conclusions

The low barriers to use of CRISPR/Cas technology, both in terms of financial costs and technological skill required, ensure that the technology will be rapidly and widely adopted and difficult to replace. As such, the technology will likely be used for the foreseeable future to introduce changes to the genomes of any number of organisms, including humans. Although the technology is relatively new, it is already being used in multiple applications, and it is only a matter of time before FDA is faced with specific requests for regulatory review of articles that utilize this technology. USDA has already reviewed several such requests, and has concluded that certain products are not subject to regulation under that agency's key statutory authority. FDA's broader statutory mandate will likely ensure that use of CRISPR/Cas technology will undergo some form of agency review prior to marketing, but specifically how FDA will approach these submissions is yet to be seen. Because of the uniqueness and novelty of such a submission, sponsoring companies will have an added burden of educating FDA, and of wading against the natural precautionary tendencies of an agency faced with a high-profile and unproven technology.

1. On its website, FDA has an infographic regarding the process of using rDNA technology to engineer animals to produce human biologics. *See* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM144055.pdf.
2. For a helpful comparison from the Genetic Literacy Project of the various methods for genetic improvement, *see* http://gmo.geneticliteracyproject.org/wp-content/uploads/2016/02/food-and-genes-large-1.png.
3. Michael Specter, *The Gene Hackers*, The New Yorker (Nov. 16, 2015), http://www.newyorker.com/magazine/2015/11/16/the-gene-hackers.
4. Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 Sci. 819 (Feb. 15, 2013).
5. Alice Park, *Life, The Remix*, TIME 42, 45 (July 4, 2016).
6. http://www.ncbi.nlm.nih.gov/pubmed/ (search "crispr" with filter for publication date between June 1, 2016 and July 7, 2016).
7. Nikhita Ajit Bolar et al., *Heterozygous Loss-of-Function SEC61A1 Mutations Cause Autosomal-Dominant Tubulo-Interstitial and Glomerulocystic Kidney Disease with Anemia*, 99 Amer. J. Hum. Genetics 174 (July 7, 2016).
8. Konrad Fisher et al., *Efficient production of multi-modified pigs for xenotransplantation by 'combineering', gene stacking and gene editing*, 6 Nature Sci. Reps. (June 29, 2016).
9. George Savidis et al., *Identification of Zika Virus and Dengue Virus Dependency Factors using Functional Genomics*, 16 Cell Reps. 232 (June 28, 2016).
10. Stefano Annunziato et al., *Modeling invasive lobular breast carcinoma by CRISPR/Cas9-mediated somatic genome editing of the mammary gland*, 30 Genes & Dev. 1470 (June 15, 2016).
11. L. Zang & R.D. Reed, *Genome editing in butterflies reveals that spalt promotes and Distal-less represses eyespot colour patterns*, 7 Nature Comms. 11,769 (June 15, 2016).
12. Alice Park, *U.K. Approves First Studies of New Gene Editing Technique CRISPR on Human Embryos*, TIME (Feb. 1, 2016).
13. James R. Clapper, Dir. of Nat'l Intelligence, Statement for the Record, Worldwide Threat Assessment of the US Intelligence Community, Senate Armed Services Committee (Feb. 9, 2016).
14. *Id.* at 9.
15. *Id.*
16. The Nat'l Acads. Of Scis., Eng'g, and Med., Internat'l Summit on Human Gene Editing, http://www.nationalacademies.org/gene-editing/gene_167925.
17. The Nat'l Acads. Of Scis., Eng'g, and Med., Introduction, http://www.nationalacademies.org/gene-editing/index.htm.
18. In March, scientists demonstrated that CRISPR/Cas could be used to not only eliminate HIV-1 from T-cells, but could also be used to confer long-term immunity from HIV-1. Rafal Kaminski et al., *Elimination of HIV-1 Genomes from Human T-lymphoid Cells by CRISPR/Cas9 Gene Editing*, 6 Nature Sci. Reps. (Mar. 4, 2016).
19. This has already been demonstrated with respect to removal of porcine endogenous retroviruses (PERVs). Luhan Yang et al., *Genome-wide inactivation of porcine endogenous retroviruses (PERVs)*, 350 Sci. 1101 (Nov. 27, 2015).
20. CRISPR has been used to develop white mushrooms that resist browning. Emily Waltz, *Gene-edited CRISPR mushroom escapes US regulation*, Nature News (Apr. 14, 2016).
21. Scientists have demonstrated the ability to use CRISPR/Cas to selectively edit the tobacco plant. Junping Gao et al., *CRISPR/Cas9-mediated targeted mutagenesis in Nicotiana tabacum*, 87 Plant Molecular Biology 99 (Jan. 2015).
22. *See* FDC Act § 201(f), (g), (s), and (rr); PHS Act § 351(i).
23. FDA, Guidance for Industry, Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs (Jan. 2009) (minor editorial changes were made in June 2015).
24. *Id.* at 5-6.
25. PPA § 403(14) and (10).
26. *See, e.g.*, Letter from Michael J. Firko, PhD, APHIS Deputy Administrator for Biotechnology Regulatory Services to Dr. Yinyong Yang, Pennsylvania State University, regarding Request for confirmation that transgene-free, CRISPR-edited mushroom is not a regulated article (Apr. 13, 2016), https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf.
27. *See* Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986).
28. *See* 80 Fed. Reg. 62,538, 62,539 (Oct. 16, 2015).
29. *Id.* at 62,540.