The functional field of food law

Reconciling the market and human rights

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26. New plant breeding technologies: US Department of Agriculture policy[1]

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Abstract

Genetically modified crops play a significant role in US agriculture. Federal statutes and regulations help to ensure that crops developed with rDNA techniques are safe to grow, to eat, and for the environment. Recent legislation requires labels for genetically modified food; new policy documents exist; and agencies are developing updated regulations. New breeding technologies, many characterized as gene editing, offer a low-cost, accessible way to insert, delete, or replace DNA to develop new varieties. CRISPR and other new breeding technologies offer promise to developers and producers. Crops produced by these technologies, which do not use rDNA techniques, may lack a 'regulatory trigger' (an applicable statute or regulation), and the US Department of Agriculture has declined regulatory jurisdiction over many varieties. The USDA issued a formal policy stating that it will not regulate organisms developed with specific new breeding technologies. A European Court of Justice decision adopted a more cautious approach that is likely to subject most varieties developed with gene editing to the GMO regulatory process. Different regulatory standards for new breeding technologies in the US and the EU may result in trade and other issues. Because innovative biotechnologies may prove critical in providing food and feed for growing populations, regulatory requirements should be flexible, adaptable to rapid scientific development, and related to the risk posed by new technologies.

Keywords: CRISPR, US regulation of gene editing, New Plant Breeding technology, USDA regulation of genetic engineering

26.1 Introduction

Since the 1980s, scientists have used recombinant DNA technology to develop new varieties of crops that offer insect resistance, herbicide tolerance, and other

[1] This Chapter is based on work supported by USDA, National Institute of Food and Agriculture, Hatch Project No. ILLU-470-348. This Chapter relies in part, with many omissions, additions and changes, on Margaret Rosso Grossman, Genetic Technology in the United States: Regulation of Crops and Their Food Products, in Dederer H.-G. and Hamburger D. (eds) Regulation of Genome Editing in Plant Biotechnology: A comparative analysis of the regulatory framework for genome-edited plants in selected countries and the EU. Springer, Heidelberg, New York, Dordrecht, London (forthcoming, 2019).

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valuable traits.[3] More recently, some new breeding technologies (NBTs), many characterized as gene editing, offer a way to 'insert, delete, or replace DNA at a specific location within a crop's DNA' by cutting DNA at a specific location using biological molecules (Jaffe, 2017). Among NBTs, CRISPR/Cas9 is particularly important, in part because it is precise, low cost, versatile, and accessible to a wide range of plant developers, including small companies, universities, and other public institutions.[4]

Genetically modified organisms (GMOs), including GM crops and their food products, are subject to extensive regulation, both in the United States and in the European Union (Grossman, 2018). Until recently NBTs faced uncertain regulatory status. In March 2018, the US Department of Agriculture (USDA) indicated that some NBTs will not be subject to regulation. Soon thereafter, in *Confédération paysanne* the European Court of Justice (ECJ) held that most varieties developed with genome editing are subject to EU measures that govern GMOs. This decision has significant implications for researchers who develop new varieties with NBTs. Moreover, the decision is likely to discourage biotechnology research in the EU and complicate international trade in the products of biotechnology.

This Chapter focuses on US Department of Agriculture regulation of bioengineering, especially organisms produced with NBTs. As background, the Chapter provides information about US production of GM crops, briefly explains US policy and regulation of GM crops and their food products, and describes recent legislation for labelling of bioengineered food. The Chapter then outlines recent developments in federal policy and some agency proposals for regulatory change. The Chapter discusses USDA policy for new breeding technologies, USDA decisions and a significant policy statement that decline to regulate some products of gene editing. After a brief discussion of the ECJ judgment in *Confédération paysanne*, the Chapter offers some concluding thoughts about regulation of innovative biotechnology.

26.2 US regulation of GM crops: a brief review

Genetically modified (GM) – or genetically engineered (GE) – crops play a significant role in US agriculture. In 2017, US producers planted 75 million hectares of GM crops, 40% of the global total of 189.8 million hectares (ISAAA, 2018). In the

[3] These crops are referred to as genetically engineered (GE, the term preferred by USDA) or, in the European Union, genetically modified (GM) or genetically modified organisms (GMOs). The term gene or genome editing applies to some NBTs such as CRISPR.

[4] CRISPR (clustered regularly interspaced short palindromic repeats) are 'segments of bacterial DNA that, when paired with a specific guide protein, such as Cas9 …, can be used to make targeted cuts in an organism's genome' (NASEM, 2016b: 1). CRISPR is a 'naturally occurring mechanism of immunity to viruses found in bacteria that involves identification and degradation of foreign DNA. This natural mechanism has been manipulated by researchers to develop genome-editing techniques' (NASEM, 2017: 4). Cas9 is CRISPR associated protein 9.

USDA estimated that biotech varieties made up 92% of corn, 94% of soy, and 94% of upland cotton (NASS, 2018: 31-33). In 2017, 100% of US sugar beets and canola were GM herbicide-tolerant varieties; GM alfalfa, a perennial crop, made up only 14.4% of harvested alfalfa acres. A few producers grew GM sweet corn, squash, and papaya, as well as non-browning apples and potatoes (ISAAA, 2018: 11-14). The United States is also a leader in authorization of GM varieties, with approvals since 1996 for 197 traits in 19 crop species of crops (ISAAA, 2018: 9). Moreover, the United States has shared significantly in income and environmental benefits from GM crops, capturing $80.3 billion of the $186.1 billion global total increase in farm income since 1996 and enjoying 'a significant reduction in the environmental impact associated with insecticide and herbicide use' as well as reduced emissions of greenhouse gases. (Brookes and Barfoot, 2017: 13, 16-17; 2018: 71) GM crops and their food products are considered safe, offering 'an unblemished record of safe use and consumption for over 20 years' (ISAAA, 2017: 1).

26.2.1 Policy

The Coordinated Framework for Regulation of Biotechnology, published in 1986 and updated in 1992, 2002, and 2017 (OSTP, 1986, 1992, 2002; US White House, 2017), established US policy for biotechnology, with a primary focus on technology using recombinant DNA (rDNA). The Coordinated Framework drew three important conclusions: products of biotechnology are not fundamentally different from conventional products; regulations should focus on the product, rather than on the process; and regulatory jurisdiction for biotechnology products should be based on their use (OSTP, 1986: 23,303-23,304). Initial regulation of GMOs relied on existing federal law, later supplemented by new laws and regulations.

The United States relies on a 'risk-based, scientifically sound approach' to regulatory approval of GM crops and their products (OSTP, 1992: 6753). Because regulation depends on characteristics of products and their intended use, three agencies govern GM crops and their products. The USDA ensures that GM crops are safe to grow; the US Environmental Protection Agency (EPA) ensures that they are safe for the environment; the US Food and Drug Administration (FDA, along with the EPA) ensures that they are safe to eat.

26.2.2 Authorization

Other publications describe the US regulatory system for GMOs in detail,[5] so the following paragraphs focus briefly on GMO authorization, before focusing on the USDA approach to NBTs.

[5] This section relies in part on Grossman, 2012; 2016b: 306-314; 2018.

The USDA's Animal and Plant Health Inspection Service (APHIS) and its Biotechnology Regulatory Services govern environmental release (field testing), interstate movement, and import of GE plants that may pose a plant pest risk.[6] The USDA regulates plant pests, broadly defined, under authority of the Plant Protection Act of 2000[7] and APHIS regulations.[8] Most GM varieties created by rDNA technology could harbour a plant pest (e.g. *Agrobacterium* used in developing the variety) and are therefore considered 'regulated' articles, which cannot be sold commercially until they are evaluated and authorized – that is, classified as 'nonregulated.' Developers carry out field trials,[9] and if trials and other data indicate that a new variety is not a plant pest and does not threaten agriculture or the environment, the developer can petition for a determination of nonregulated status. If APHIS concludes that the GM variety poses no environmental or agricultural risk, APHIS will grant nonregulated status and then has no further regulatory jurisdiction over the variety (NASEM, 2017: 15). By September 2018, APHIS had issued 125 determinations of nonregulated status (APHIS, 2018d). Before a new variety can move freely in commerce, however, the developer must comply with EPA and FDA requirements.

The EPA regulates GE plants with pesticidal substances under authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[10] and governs pesticide residues in GE foods under the Food, Drug and Cosmetic Act (FDCA).[11] No pesticide can be sold or used in the United States until it is registered. Plant incorporated protectants (PIPs) – pesticidal substances produced by plants (e.g. the insecticide *Bacillus thuringiensis, Bt*) – are governed by EPA regulations,[12] and the developer must demonstrate, after field tests, that the pesticide will not 'cause unreasonable adverse effects on the environment.'[13] In the registration process, the EPA evaluates data on the efficacy, safety, and environmental effects of PIPs. Even after a pesticide is registered, EPA can impose requirements for its use and for post-market monitoring. Under the FDCA, raw or processed food with a pesticide residue (including a PIP) is considered adulterated; it cannot be sold in interstate commerce unless the residue meets an established tolerance or is exempt from the tolerance requirement.[14] For most PIPs in GM crops (e.g.

[6] For laboratory research, National Institutes of Health (NIH) guidelines apply. (NIH, 2016: 105-116 and Appendix P). See Miller, 2018 for criticism of NIH overregulation.
[7] 7 United States Code (USC) §§ 7701-7772 (replacing the Plant Pest and Plant Quarantine Acts).
[8] 7 Code of Federal Regulations (CFR) part 340. On plant pests, see 7 CFR §§ 340.1, 340.2.
[9] Between June 1987 and December 2018, APHIS reported 21,432 notifications and permits (APHIS, 2018a).
[10] 7 USC §§ 136-136y.
[11] 21 USC §§ 301-399f, §§ 2201-2252.
[12] 40 CFR parts 154 (pesticide registration), 172 (experimental use permits), and 174 (PIPs).
[13] 7 USC § 136a(c)(5); § 136(bb), defining unreasonable adverse effects.
[14] 21 USC § 346a. A tolerance is a legal limit on the maximum amount of a substance in or on food; scientific data must establish that the tolerance is safe (not toxic or allergenic). Safe is defined at 21 USC § 346a(b)(2).

Bt in corn, cotton, and soy), EPA regulations grant temporary and permanent exemptions from the tolerance requirement.[15]

The FDA governs food safety but generally does not conduct pre-market safety review of new plant foods. Instead, developers have legal responsibility to evaluate safety and to comply with the FDCA and FDA regulations. The FDA's focus for GM foods is the food product – its characteristics and intended use – rather than the process of development (FDA, 1992: 22,984-22,985). Relying on the concept of substantial equivalence, the FDA requires premarket review only if a GM food differs in nutritional components from its conventional counterpart (FDA, 1992: 22,992).

To ensure food safety, the FDA relies primarily on statutory provisions that prohibit adulteration and misbranding of food and govern food additives.[16] Under the FDCA, a food is adulterated if it contains, among other things, an unsafe additive. Food additives are considered unsafe and therefore adulterated until they have been granted premarket approval or are exempt from approval.[17] The FDCA definition of food additive, however, excludes substances that are 'generally recognized as safe' (GRAS).[18] Most GM foods are considered GRAS (FDA, 1992: 22,990) and therefore exempt from premarket review.[19] The FDA's 2016 GRAS regulations[20] impose stringent scientific requirements for a GRAS determination, but manufacturers themselves make that determination, and notification to FDA is voluntary. Although the FDA does not mandate review of new GM plant foods, early food safety evaluations (FDA, 2006) and biotechnology consultations (FDA, 1997) help FDA to identify unresolved scientific and regulatory issues. Developers of GM foods seek these voluntary consultations, perhaps to avoid liability triggered by unsafe foods.[21]

26.2.3 Labels for GM Food: 2016 Federal Law

Food labelling requirements in the United States (e.g. nutrition labels) apply to all foods, including GM foods. The FDA, unlike regulators in the EU, did not require special labels to inform consumers of GM content.[22] Demand for labels

[15] 40 CFR §§ 174.501-174.539 (listing exemptions from the tolerance requirement).
[16] 21 USC §§ 342, 343, 348.
[17] 21 USC § 348; 21 CFR part 170.
[18] 21 USC § 321(s).
[19] Alliance for Bio-Integrity v. Shalala (2000), 116 F. Supp. 2d 166 (D. D.C.), upheld FDA's presumption of GRAS status for GM foods.
[20] 21 CFR §§ 170.203-170.285. See FDA, 2016; Grossman, 2017.
[21] By March 2018, the FDA had completed 16 early food safety evaluations (with 2 others withdrawn) (FDA, 2018a), and by December 2018, the agency had completed 183 biotechnology consultations on food from GM plants (FDA, 2018b).
[22] For more details on labeling see Grossman, 2016a and references therein; on voluntary labelling see FDA, 2015.

for GM foods led Congress to enact the National Bioengineered Food Disclosure Standard.[23] The law pre-empts state and local labelling laws and requires labels for statutorily-defined bioengineered food and food with bioengineered ingredients.[24] The term 'bioengineering' refers to food modified through *in vitro* rDNA techniques if the modification could not occur through conventional breeding or be found in nature.[25] Thus, the law seems to exclude labelling for many NBTs.

The Disclosure Standard assigned responsibility for implementing the law to the USDA, acting through its Agricultural Marketing Service (AMS). By regulation AMS had to determine when a food is bioengineered, establish the GE threshold for labelling, and prescribe the form of disclosure. AMS published draft regulations in May 2018 (AMS, 2018a) and final regulations in December 2018 (AMS, 2018b).[26] The final regulations identify foods subject to disclosure – that is, food with detectable genetic material from bioengineering – and allow a 5% threshold for inadvertent or technically unavoidable bioengineered presence of each ingredient. Regulations establish, among other requirements, exemptions, standards for detectability, mechanisms for disclosure, and compliance deadlines. AMS regulations, like the Disclosure Standard, do not address foods produced by gene editing. The final AMS regulations may leave unanswered questions and incomplete disclosure (Grossman, 2016a: 504-507).

26.2.4 New regulatory directions?

Policy developments during the Obama administration pointed toward a modernized regulatory system for biotechnology, but little regulatory change has occurred. An Executive Order instructed regulatory agencies to strive for scientific integrity and to use the 'most innovative and least burdensome tools' for regulation (Obama, 2011: 1-2), and a memorandum from the Office of Science and Technology Policy (OSTP) set out principles for regulating emerging technologies, including genetic engineering. Regulation should not unjustifiably inhibit innovation, stigmatize new technologies, or create barriers to trade, and risk management requirements should be appropriate for the degree of risk of the new technology (Holdren *et al.,* 2011: 1-2). The Obama administration formed a Biotechnology Working Group and directed that group to develop two documents, an updated Coordinated Framework and a long-term biotechnology strategy, and to commission an independent analysis to identify risks (or lack of risks) from future biotechnology products (Holdren *et al.,* 2015: 4-5).[27]

[23] 7 USC §§ 1639-1639c, 1639i-1639j.
[24] The Disclosure Standard applies to most food as defined by 21 USC § 321(f).
[25] 7 USC § 1639(1).
[26] The USDA did not meet the 29 July 2018 statutory deadline for promulgation of final regulations.
[27] A report from the National Academies of Science, Engineering, and Medicine (NASEM, 2017) fulfilled this requirement.

The National Strategy for Modernizing the Regulatory System for Biotechnology Products described existing mechanisms, activities, and future plans of the major regulatory agencies for increasing transparency, predictability and efficiency, and supporting the science of biotechnology (US White House, 2016). The Update to the Coordinated Framework for the Regulation of Biotechnology (US White House, 2017) indicated that regulation will continue to focus on the intended uses of products rather than the process of development and also that characteristics and uses of the product and the environment should determine risk. Moreover, 'the regulatory system should distinguish between those biotechnology products that require a certain level of Federal oversight and those that do not' (US White House: 8). The Update did not recommend measures to address risks of new technologies. Instead, the 2017 Coordinated Framework restated the current authority and responsibilities of the USDA, EPA, and FDA in regulation of products of biotechnology (US White House: 9-10), described agency cooperation in the regulation of biotechnology products, and presented hypothetical case studies as practical examples of regulation for GM developers (US White House: 39-51).

Despite the 2015 charge to the Biotechnology Working Group, which included a strategy for regulating innovative technologies, its work represents a 'missed opportunity' for restructuring the regulatory system (Kuzma, 2016: 1211). The National Strategy failed to describe plans for assessing the risks of future products of biotechnology, and the 2017 Coordinated Framework provided no regulatory guidance for new technologies like CRISPR and other forms of genome editing (Peck, 2017: 324). Moreover, the Update did not meet the goals of the 2015 memorandum on modernizing the US biotechnology regulatory system (CAST, 2018: 7).

Regulation of biotechnology has changed little in recent years. In January 2017, APHIS published proposed amendments to its 1987 rule governing the release and commercialization of GE organisms (APHIS, 2017a). APHIS noted that most GE technologies do not pose plant pest risks, but that some technologies that use no plant pests as donor or recipient organisms could pose risks. APHIS asserted that GE plants should also be evaluated as noxious weeds (APHIS, 2017a: 7009-7011). GE biological control agents and GE plants that produce plant-made industrial and pharmaceutical products require regulation to protect the food supply. The proposed rule would have altered USDA's 'regulate first/analyse later' approach because it would first assess new organisms and then regulate only organisms that posed risks. Public comments on the proposed rule revealed substantial disagreement, and APHIS withdrew the proposal in November 2017 (APHIS, 2017b).

APHIS is again considering amendments to its GMO regulations. In June 2018, the agency published notice of its intention to prepare an Environmental Impact

Statement[28] to analyse proposed new GMO regulations (APHIS, 2018e). In new regulations, APHIS intends to address advances in biotechnology, protect plant health more effectively with a focus on risk rather the methods of production, make regulation more transparent, and remove unnecessary regulatory burdens.

In January 2017, the FDA requested comments about genome editing in new plant varieties used for food (FDA, 2017). The FDA did not propose new regulatory measures, but instead sought information about food safety risks from new technologies, data relevant to safety assessment and the regulatory status of these new organisms, and advice about voluntary consultations or other methods of informing the agency about new products. In May 2018, the FDA created a Biotechnology Working Group, intended to promote innovation, strengthen communication, and support regulatory alignment with domestic and international partners (Gottlieb and Abram, 2018).

26.3 US Regulation of new breeding technologies

NBTs offer precision, accessibility, and diversity, but they raise regulatory issues. As the National Academies indicated, new 'genetic-engineering technologies challenge most existing regulatory systems by blurring the distinction between genetic engineering and conventional plant breeding while enabling increasingly profound alterations of plant metabolism, composition, and ecology' (NASEM, 2016a: 26).

Agency jurisdiction over GM technology requires a 'regulatory trigger' – that is, an applicable statute or regulation. USDA has authority over plant pests under the Plant Protection Act, and APHIS regulations define plant pests broadly. But APHIS regulations define genetic engineering narrowly, as 'genetic modification of organisms by recombinant DNA techniques.'[29] This definition seems to exclude many plants developed with NBTs.[30] Because EPA authority extends only to GM varieties with pesticidal properties, that agency will not regulate varieties that contain 'no new genetic material from a non-sexually compatible source' (NASEM, 2016a: 498). The FDA defines genetic engineering more broadly than USDA (FDA, 1992: 22,982), but NBTs do not usually add genetic material to food, so FDA may lack jurisdiction in the absence of food additives that are not GRAS (Peck, 2017: 322). Moreover, FDA relies on voluntary consultation unless a new GM variety is allergenic, toxic, or not substantially equivalent to its comparator. Thus, federal statutes and regulations may lack a regulatory trigger for jurisdiction over NBTs.

[28] The National Environmental Policy Act, 42 USC §§ 4321-4370f, requires federal agencies to prepare an EIS for 'major federal actions significantly affecting the quality of the human environment' § 4332(2)(C).
[29] 7 CFR § 340.1.
[30] APHIS authority to govern noxious weeds applies, even if the new variety is not governed by GMO regulations. 7 CFR part 360.

The USDA's role in evaluating NBTs is critical, and its recent decisions are significant for both NBT developers and US trading partners. As indicated just above, the USDA defines a regulated article or product in terms of genetic modification with rDNA techniques. Genome editing, however, does not always transfer genetic material, but can modify or delete genetic traits without inserting new material. (Peck, 2017: 321). Thus, USDA's definition is likely to exclude many products of NBTs. Similarly, under the Bioengineered Disclosure Standard, implemented by USDA, labelling applies to food modified by '*in vitro* recombinant deoxyribonucleic acid (DNA) techniques' with modifications not possible through 'conventional breeding or found in nature.'[31]

Process-based regulations are 'always a step behind the introduction of new techniques' (Conko *et al.*, 2016: 502), particularly if the regulatory trigger is based on the process of development, rather than the product (NASEM, 2016a: 493). Moreover, traditional types of risk assessment, which assume that a new GM crop was created with rDNA technology, may not adequately address risk characteristics of crops produced with new technologies (NASEM, 2016a: 494). The lack of markers that verify the use of some NBTs (for example ZFN, TALEN, and CRISPR) will raise additional regulatory and trade issues (Smyth, 2017: 81).

26.3.1 Am I regulated?

An individual or company with plans to release a regulated organism into the environment, move it interstate, or import it must obtain authorization (nonregulated status) from USDA. A developer who is unsure whether a new organism is regulated can request a determination from APHIS Biotechnology Regulatory Services (BRS) using 'Am I regulated?' (BRS, 2017). This procedure alerts APHIS to new developments and, via review, informs developers about their legal obligations. The procedure requires a letter of inquiry accompanied by information about the developer and the intended activity (release or movement); descriptions of the intended phenotype, genetic change (insertion, deletion, substitution), vector or vector agent (biolistic, nuclease, *Agrobacterium*); and other scientific information. BRS responds to indicate the regulatory status of the new organism.

BRS maintains a database of letters of inquiry and its responses. Between January 2011 and November 2018, BRS had received and responded to 74 inquiries. BRS concluded that many, but not all, new organisms were not regulated – and thus not subject to the GMO regulatory process – because they included no plant pest or could be created by conventional breeding (APHIS, 2018b).[32]

[31] 7 USC § 1639(1).

[32] The USDA APHIS database includes 'Am I regulated?' inquiries and BRS responses since 2011. Citations to APHIS, 2018b link to these documents for each variety.

26.3.2 USDA decisions

Using 'Am I regulated?' USDA, acting through BRS, has declined regulatory jurisdiction over varieties developed with new genetic engineering technologies, including OMM (oligonucleotide mediated mutagenesis), ZFN (zinc finger nuclease), EMN (engineered mega nuclease), and TALEN (transcriptional activator-like effector nuclease) (Wolt *et al.*, 2016: 511, 515). Since about 2010, USDA has declined to regulate numerous organisms developed with NBTs that have no plant-pest components and therefore do not pose a plant-pest risk (Waltz, 2016: 293; NASEM, 2016a: 495).[33] New organisms are subject to FDA and EPA requirements,[34] if any, and import is subject to plant protection and quarantine requirements.

For example, BRS determined that Dow AgroScience's ZFN-12 maize, engineered with zinc finger nuclease technology to reduce production of phytate (an anti-nutritional component of feed grain) was not regulated (Gregoire, 2010). BRS declined to regulate several varieties engineered with TALEN technology: the Simplot low-PPO5 potato engineered to resist black spot, a Calyxt potato, and a Calyxt nutritionally-enhanced wheat. BRS also declined to regulate varieties developed biolistically: e.g. maize, cisgenic rice (subject to further analysis for weediness), and soybeans. 'Am I regulated?' inquiries and responses reflect careful review; recently BRS decided that a new variety, a plant pathogen made less virulent by gene deletion, remains regulated as a plant pest.[35]

Varieties developed with CRISPR/Cas9 technology may also lack a plant-pest regulatory trigger. Some of these NBT varieties were developed by small companies, university researchers, and others for whom the high cost of the GMO regulatory system would be prohibitive. In 2016, the agency evaluated the first two inquiries for varieties developed with CRISPR/Cas9 technology: a white button mushroom with an anti-browning phenotype developed at the University of Pennsylvania and a high-yielding waxy corn developed by DuPont Pioneer (APHIS, 2018b). These organisms do not include 'introduced genetic material' and are not plant pests; therefore, they are not regulated articles nor are they regulated as noxious weeds.[36]

Other CRISPR/Cas9 organisms that BRS declined to regulate include a false flax (*Camelina sativa*), used as a biofuel and to replace fish oil for aquaculture,[37] a

[33] Other techniques include cisgenesis and intragenesis, developed in part because of 'legislative, regulatory, marketing, and public-perception concerns' (NASEM, 2016a: 357).
[34] Developers of new GM foods normally participate in FDA's voluntary biotechnology consultations, but the agency's database of consultations does not yet include innovative varieties. See FDA, 2018a.
[35] *Erwinia amylovora*, modified for application to apple trees, remained a plant pathogen, which is a plant pest.
[36] 7 CFR part 340; 7 CFR part 360.
[37] Yield10 Bioscience indicated that their testing and data collection took two years, and the USDA decision, two months. They saved time and spent far less than the $30-$50 million that would have been required to comply with more comprehensive GM regulation (Waltz, 2018).

soybean (*Glycine max*) that is salt-tolerant and resistant to drought, a DuPont Pioneer corn with improved resistance to northern leaf blight, a University of Florida tomato variety, an Iowa State University maize variety, and an Illinois State University pennycress. BRS decisions indicate careful consideration. For example, in 2017, BRS determined that a variety of *Setaria viridis* (bristlegrass) was not a regulated article, but had potential to be a problematic weed in agricultural environments. Therefore, regulators recommended maintenance of isolation distances to avoid possible crosses with *Setaria italica* (foxtail millet) used for hay. Similarly, BRS instructed the developer of a new *Camelina* variety to develop stewardship measures to control gene flow between the new variety and conventional *Camelina*. (APHIS, 2018b)

26.3.3 USDA policy statement

In March 2018, USDA issued a formal statement about its regulation of innovative plant breeding. The statement noted that plants developed with NBTs, including genome editing, offer benefits for both farmers and consumers and that varieties developed with NBTs are often indistinguishable from plants developed with traditional breeding. (APHIS, 2018c) In a press release, the US Secretary of Agriculture noted that new plant breeding tools can 'introduce new plant traits more quickly and precisely, potentially saving years or even decades in bringing needed new varieties to farmers' (USDA, 2018).

USDA articulated its policy:

> Under its biotechnology regulations, USDA does not currently regulate, or have any plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are developed without the use of a plant pest as the donor or vector and they are not themselves plant pests. (APHIS, 2018c)

Organisms that USDA will not regulate include those developed with deletions of any size, single base pair substitutions, insertions from compatible plant relatives,[38] and complete null segregants.[39] USDA promised to advance a 'science-based and practical approach that protects plant health while allowing for technical advancements' (APHIS, 2018c). The decision confirms, as a National Academies report insisted, that 'any attempt by regulators to define the scope of a regulatory system through the definition of specific technologies will be rapidly outmoded by new approaches' (NASEM, 2016a: 509).

[38] USDA explains: 'the change to the plant solely introduces nucleic acid sequences from a compatible relative that could otherwise cross with the recipient organism and produce viable progeny through traditional breeding' (APHIS, 2018c).

[39] USDA explains: 'off-spring of a genetically engineered plant that does not retain the change of its parent' (APHIS, 2018c).

USDA's decision not to regulate most crops developed with CRISPR and other NBTs is significant for developers and producers, because new varieties will be available at a lower cost for developers, including small companies and academic researchers, and more quickly for producers. Development of new varieties is expensive, and regulatory requirements for GMOs impose significant costs. Compliance with those requirements may cost as much as $30-$50 million (Waltz, 2018: 6). Moreover, the regulatory process is time-consuming. One study found that assessment of scientific evidence in the United States took 686 days; another study of 95 applications calculated the mean time for the whole approval process (field trials, petition process) as 1,321 days between 1988 and 1997 and 2,467 days between 1998 and 2016 (Smart *et al.*, 2017: 183, 187, 192).[40]

26.4 European Court of Justice: *Confédération paysanne*

26.4.1 ECJ Judgment

A recent interpretation of EU legislation that governs deliberate release of GMOs resulted in a more cautious approach to NBTs. In July 2018, the European Court of Justice issued its long-awaited judgment in *Confédération paysanne*[41] The French Council of State had requested a preliminary ruling in proceedings that challenged the refusal by the French Prime Minister and Minister for Agriculture to revoke national legislation that did not classify organisms developed by mutagenesis as GMOs and the related refusal to ban cultivation of mutagenic herbicide-tolerant varieties of rape (*Confédération*, para. 2). The ECJ ruling interprets Directive 2001/18/EC on the deliberate release of GMOs,[42] as well as Directive 2002/53/EC on the common catalogue of varieties of agricultural plant species.[43]

The French Council of State referred four questions for preliminary ruling. The threshold question is whether organisms obtained by mutagenesis are subject to the EU authorization process for GMOs. Directive 2001/18 exempts from regulation as GMOs certain GM organisms obtained by techniques of genetic modification listed in an annex; mutagenesis is one of those techniques.[44] The extent of the mutagenesis exemption was at issue.

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[40] In the EU, the mean approval time for authorized organisms from 1995 to 2015 was 1,758 days (Smart *et al.*, 2017).

[41] Case C-528/16, *Confédération paysanne v. Premier ministre*, European Court of Justice, Grand Chamber (25 July 2018).

[42] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, OJ 2001 L 106: 1.

[43] Council Directive 2002/53/EC of 13 June 2002 on the common catalogue of varieties of agricultural plant species, OJ 2002 L 193: 1, as amended by Regulation 1829/2003/EC of 22 September 2003, OJ 2003, L 268: 1.

[44] Directive 2001/18, art. 3(1) and Annex I B. This discussion summarizes the conclusions in the Bobek Opinion and ECJ Judgment.

The thoughtful opinion of Advocate General Bobek,[45] delivered 18 January 2018, suggested that the Court should answer the threshold question by deciding that organisms obtained by mutagenesis can be GMOs but that under the exemption, all organisms developed by mutagenesis (not only organisms from classical mutagenesis techniques in use in 2001) should be exempt from GMO legislation with its requirements for risk assessment, traceability, labelling, monitoring, if those mutagenic organisms do not use rNA molecules or certain GMOs (Bobek opinion, para. 107). Bobek asserted that the 'EU legislature could not ignore technological progress' (Bobek opinion, para. 77).

Although the European Court of Justice often follows the suggested conclusions of the Advocate General, in this case, the judgment of the Grand Chamber (15 judges) came to a more restrictive interpretation of Directive 2001/18. The ECJ agreed that organisms obtained by 'techniques/methods of mutagenesis constitute GMOs' under the Directive (*Confédération*, para. 54). But the Court also held that only mutagenic organisms obtained by techniques/methods that 'have conventionally been used in a number of applications and have a long safety record' are excluded from regulation under from the Directive (*Confédération*, para. 54). Although the meaning of 'a long safety record' raises questions, the ECJ judgment seems to restrict the mutagenesis exemption to classical mutagenesis using techniques available when Directive 2001/18 was enacted.

The ECJ addressed the remaining questions referred by the French Council of State. As to the second question about application of Directive 2002/53 that governs the common catalogue of plant varieties, the Court applied the same standard, concluding that only mutagenic varieties obtained by conventional techniques with a long safety record are exempt from obligations for environmental risk assessment in that Directive (*Confédération*, para. 68).[46] The third question focused on Member State discretion to regulate mutagenic organisms excluded from regulation as GMOs under Directive 2001/18. The ECJ concluded that Member States may regulate organisms obtained by conventional mutagenesis, as long as the State complies with other obligations of EU law, including free movement of goods (*Confédération*, para. 82).[47] In light of its decision that mutagenic organisms created by new techniques are subject to regulation as GMOs, the Court did not address the fourth question, which focused on whether a broad exemption for mutagenic organisms would violate the precautionary principle (*Confédération*, para. 84).

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[45] Case C-528/16, *Confédération paysanne v. Premier ministre,* Opinion of Advocate General Bobek (18 January 2018).

[46] Bobek had suggested that mutagenic organisms exempt under Directive 2001/18 should also be exempt from requirements for GMOs under Directive 2002/53 (para. 167), and that the precautionary principle does not affect the validity of the exemption for mutagenesis in Directive 2001/18 (para. 152).

[47] Bobek agreed. He suggested that the ECJ should conclude that Directive 2001/18 does not preclude Member State regulation of mutagenesis, if they observe EU law (Bobeck opinion, paras. 123-124).

The ECJ judgment will require developers of certain varieties (those using the types of mutagenesis at issue in the case) to comply with EU measures that govern GMOs. The ECJ's processed-based interpretation of the Directive's definition of GMOs (*Confédération*, paras. 27-29) may extend that requirement to other NBTs.[48] This decision, criticized by academic and industry researchers, is likely to discourage advanced plant breeding in the EU and to exclude some small-company and university researchers without the means to finance the cost of regulation of their new varieties as GMOs. Even large companies are unlikely to develop gene-edited crops to market in in the EU (Reuters, 2018). As an industry spokesman indicated, '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.' (Byrne, 2018, quoting Garlich von Essen, European Seed Association).

26.4.2 USDA response

The Court issued its judgment a few months after the USDA had formally announced its intention not to regulate many products of gene editing. In response to the ECJ judgment, the US Secretary of Agriculture issued a statement that encouraged 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' (Perdue, 2018). Noting the promise of innovations such as gene editing for consumers and farmers, the Secretary stated that:

> Government policies should encourage scientific innovation without creating unnecessary barriers or unjustifiably stigmatizing new technologies. Unfortunately, this week's ECJ ruling is a setback in this regard in that it narrowly considers newer genome editing methods to be within the scope of the European Union's regressive and outdated regulations governing genetically modified organisms. (Perdue, 2018)

This rather critical response reflects the Secretary's belief that '[t]he global regulatory treatment of genome-edited agricultural products has strategic innovation and trade implications for U.S. agriculture.' Therefore, '[i]n light of the ECJ ruling, USDA will re-double its efforts to work with partners globally towards science- and risk-based regulatory approaches' (Perdue, 2018).

26.5 Conclusion

US regulation of biotechnology is complex, fragmented, time-consuming, and expensive, with developers subject to regulation in two or even three administrative

[48] For this insight the author thanks David Hamburger, Legal Research Assistant, University of Passau. Germany.

agencies.[49] Documents intended to modernize the US regulatory system failed, among other things, to provide guidance for regulation of new technologies, including NBTs, and potential new risks. The Biotechnology Working Group's 2016 National Strategy recommended that regulation focus on products that require federal oversight, and its 2017 Coordinated Framework outlined agency responsibility and plans for coordination. A number of scholars have made sensible recommendations for regulatory changes (e.g. Conko *et al.,* 2016; Peck, 2017; Podevin *et al.*, 2012), and the USDA has again begun the process of modernizing biotechnology regulation.

The National Academies of Sciences, Engineering, and Medicine indicated that rapid developments in biotechnology in the past decade suggest that the 'scale, scope, complexity, and tempo of biotechnology are likely to increase in the next 5-10 years' (NASEM, 2017: 172).[50] These new developments may pose regulatory challenges for both jurisdiction and risk analysis (NASEM, 2017: 11). Regulatory definitions, established to govern rDNA technology, are narrow and exclude some innovative organisms, including varieties developed with NBTs, and current methods of risk assessment are not necessarily appropriate. The US Disclosure Standard and final regulations for labelling GM food also seems to exclude most NBTs. Thus, varieties developed with new technologies do not always fit within 'product definitions, regulatory frameworks and risk assessment approaches' used for GM products (Podevin *et al.*, 2012: 1057).

The National Academies recommended that regulation focus on products of biotechnology, rather than the process of development, and consider the risk of novel characteristics to health or environment, the extent of uncertainty about severity of harm, and potential for exposure. New products without intended traits or alterations that raise health or environment concerns should face no further testing, but products with potential for health or environmental effects or with significant differences from comparators should face further safety testing[51] (NASEM, 2016a: 26-27, 513).

Because of a perceived lack of risk, the USDA declined to regulate varieties developed with CRISPR/Cas9 and other NBTs that are not plant pests or weedy. USDA's important March 2018 statement formalized its decision not to regulate specific types of crops developed with NBTs. In contrast, the July 2018 ECJ judgment in *Confédération paysanne* held that certain varieties developed with genome

[49] Indeed, a recent criticism characterized regulation of GM crops as 'a scientifically unjustified barrier to agricultural innovation' (CAST, 2018: 16).

[50] Scope refers to new types biotechnology products not yet seen by regulators; scale, to the number of products and variants of products; complexity, to the number of traits in a single product and interactions between elements in a product (NASEM, 2017: 139).

[51] The National Academies also recommended that policymakers address socio-economic, as well as scientific, issues and facilitate communication with the public.

editing are subject to EU regulations that govern GMOs. This decision is likely to have significant implications for breeders using CRISPR/Cas9 and other NBTs, and it promises to complicate trade in the products of biotechnology. Asynchronous authorization of GM crop varieties has affected crop developers, farmers, and others; trade disruption has caused rejection of shipments, changed trade patterns, and economic losses. New trade issues could arise from varieties obtained with NBTs that are not regulated in the United States but are subject to GMO regulation in the European Union. NBT varieties that leave no markers also pose risks to trade.

Innovative biotechnologies, like CRISPR/Cas9 and other types of gene editing, may prove critical in providing food and feed for growing populations. Less costly and more precise than some other technologies, CRISPR is available both to large corporate seed companies and to small enterprises, public research bodies, and others that develop varieties without large global markets (CAST, 2018: 2-3, 11-12, 15).[52] For small companies and public institutions, the 'unnecessarily complicated, onerous, and unscientific regulatory system presents a near insurmountable barrier' to commercialization (CAST, 2018: 16).

Thoughtful commentators insisted that 'there are high-risk organisms, but no high-risk techniques,' and argued for regulatory measures grounded in data and experience and focused on the end product, rather than on the type of technology (Conko *et al.*, 2016: 498).[53] Thus, to encourage innovation and protect human health and the environment in the United States and in other nations, regulatory requirements for innovative biotechnology should be flexible, adaptable to the rapid development of technology, and related closely to the level of risk presented by products of innovative technologies (Conko *et al.,* 2016: 502). Indeed, 'regulators should think twice before regulating the risks associated with new technologies. Innovation is important to any society, and innovation requires risk-taking.' Regulators should ask 'whether we are better off without the proposed restrictions, or with a more modest regime. Not all risks can and should be regulated; some risks are well worth taking' (Bergkamp, 2017: 62-63).

[52] Companies that develop crops with a large global market – often annual field crops – can afford 'burdensome and costly regulatory requirements,' and these companies may not develop crops for farmers in developing countries (Conko *et al.,* 2016: 501-502). High costs and data demands of the regulatory process may inhibit development of small-market, specialty, and perennial crops (CAST, 2018: 12).

[53] Miller, 2018: 45 asserted that the 'focus on the technique(s) has caused no end of mischief. It has turned on its head the fundamental principle of regulation – proportionality – which dictates that the degree of scrutiny should be proportional to the perceived degree of risk,' leading to over-regulation of biotechnology.

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