# Outlaws, old laws and no laws: the prospects of gene editing for agriculture in United States

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The advent of genome-edited products that are nearing commercialization in agriculture has highlighted that the US biotechnology regulatory system has not kept pace with technological advances. Of the three agencies that regulate engineered crops and animals for agriculture, only one has indicated how it will regulate edited plants. The Food and Drug Administration can regulate any plant, but has not indicated if it will single out edited plants. The US Department of Agriculture currently has no authority over edited plants when the edit is a deletion or does not contain any added DNA from a plant pest. Depending on how the statutes are interpreted, the Environmental Protection Agency might be able to regulate plants edited to tolerate pests and diseases. Labeling requirements also remain undefined. Regardless, sectors of the industry and some consumer groups are uneasy over editing technology, and may be the ultimate arbiters of whether edited products make it to market.

#### Old laws and no new laws regulate biotechnology in United States

Science and technology move at a far greater pace than legal frameworks. Hence it is not surprising that products developed through gene editing have made the news recently, in particular, because these products appear to bypass regulatory oversight in the United States (Camacho et al. 2014, Pollack 2015, Waltz 2016). Key parts of the US regulatory system have not yet determined whether or not genome-edited products need to be regulated, much less how to regulate them. Accordingly, the goals in this minireview are to explain why the US Department of Agriculture (USDA) does not exercise regulatory authority over these first products, and to assess the future regulatory landscape in United States for gene-edited crop products.

To understand the potential regulations for geneediting in agriculture, it is necessary to first understand

how agricultural plants and animals of rDNA are regulated in United States. These fall under the Coordinated Framework for Biotechnology, which was established in 1986 by the White House Office of Science and Technology Policy (OSTP). The premise behind the Coordinated Framework is that no new laws were needed to regulate products made with rDNA. Instead, these could be regulated under existing laws. Among the applicable laws, three were seen as particularly amenable to the regulation of biotechnology: the Federal Plant Protection Act (PPA), the Federal Food, Drug and Cosmetic Act and the Federal insecticide, Fungicide, and Rodenticide Act (FIFRA). These laws empower, respectively, the USDA, the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) to regulate different aspects of crops produced with rDNA (Fig. 1).

Abbreviations – AMS, Agricultural Marketing Service; APHIS, Animal and Plant Health Inspection Service; CVM, Center for Veterinary Medicine; EPA, US Environmental Protection Agency; FDA, US Food and Drug Administration; FIFRA, the Federal insecticide, Fungicide, and Rodenticide Act; NASEM, National Academies of Sciences, Engineering, and Medicine; OSTP, Office of Science and Technology Policy; PIP, plant-incorporated protectant; PPA, Plant Protection Act; rDNA, recombinant DNA; USDA, United States Department of Agriculture.



Fig. 1. The coordinated framework for biotechnology regulation in United States. A crop produced with recombinant DNA could be regulated by no. one, two, or all three agencies, depending on the crop and the introduced trait. For example, a flower modified for a new color using Agrobacterium is only regulated by the USDA, while a maize plant engineered for insect resistance is regulated by all three agencies. The USDA cannot regulate edited plants that do not contain pathogen-derived DNA or DNA introduced with Agrobacterium, as long as the plants are not noxious weeds. The extent to which FDA and EPA will regulate edited plants remains unresolved as of this writing.

#### The USDA position – the plant pest concept and why edited plants are not outlaws

The PPA authorizes the USDA to regulate plant pests through Animal and Plant Health Inspection Service (APHIS). To make the PPA fit for purpose, the USDA-APHIS declared transgenic plants to be plant pests, and therefore 'regulated articles' until shown otherwise. The plant pest claim was convenient, because in the initial days of engineering, it was routine to use DNA from viruses and bacteria that were known plant pathogens. Examples include T-DNA borders, the 35S promoter from the cauliflower mosaic virus and the nopaline synthase (NOS) terminator from Agrobacterium. Thus, by adding DNA from a plant pest to a plant, the whole plant legally became suspect of being plant pest and could therefore be regulated. Even if no pathogen-derived DNA was added to a plant, as long as the transfer was mediated by Agrobacterium, which is a plant pest, the resulting plant can still be regulated as a plant pest.

Genome editing does not always fit under the plant pest concept. There is a misconception that the USDA-APHIS deregulated, or chose not to regulate, the first crops modified by genome editing. In reality, these plants were never regulated in first place because they are outside the scope of regulations. The reason is that USDA lacks the legal authority to regulate them because they do not contain pest-derived DNA or DNA added using *Agrobacterium*-mediated transformation. Even if pathogen-derived DNA or *Agrobacterium*-mediated transformation is used, as long as the transgene is segregated out and not present in the final product, the USDA lacks legal authority for its regulation. In the context of edited plants, although a transgenic step is frequently involved in their generation, the USDA cannot regulate them as long as pathogen-derived DNA is not in the final product. The same applies for the absence of DNA added using *Agrobacterium*.

This lack of authority explains why the USDA has refrained from reviewing edited products to date. Nevertheless, edited products that contain endonuclease genes, template DNA or directed-transgene insertions remain covered by regulations if the DNA originated from a plant pest. Any product developer who is uncertain if their product is covered by USDA regulations may consult with the USDA through its 'Am I Regulated?' process (USDA 2017a). Letters received to date by the USDA on genome-edited products are listed in Table 1.

The USDA's lack of legal authority to regulate edited products, and the publicity generated as a consequence (Cyranoski 2015, Kim and Kim 2016, Kuzma 2016), probably helped prompt the OSTP (2015) to instruct the

**Table 1.** 'Am I regulated?' letters of inquiry received by the USDA as 1 April 2018 inquiring where genome-edited products were covered by USDA regulations. When transgenes were involved, they have been segregated out in the final product (necessary if they contained pathogen-derived DNA or were introduced with *Agrobacterium*). These letters are sent when developers are unsure if their product is regulated by the USDA. Exemption from USDA coverage does not imply exemption from the usual phytosanitary requirements or from FDA or EPA regulations on crops produced with recombinant DNA. <sup>a</sup>Information obtained from the company website rather than an 'am I regulated?' letter. The methodology used by Cibus is from Sauer et al. 2016.

Crop	Trait	Developer	Technology used	Edited change
Alfalfa	Low lignin	Calxyt	TALEN	Knock out (KO)
Button mushroom	Non-browing	PennState University	CRISPR	КО
Camelina	Confidential	Yield 10 Bioscience	CRISPR	КО
Canola <sup>a</sup>	Sulfonylurea herbicide tolerance <sup>a</sup>	Cibus	Oligonucleotide directed mutagenesis (ODS)	Base-pair replacement
Flax <sup>a</sup>	Glyphosate herbicide tolerance <sup>a</sup>	Cibus	ODS	Base-pair replacement
Green foxtail	Flowering time	Danforth	CRISPR	КО
Maize	Increased yield	Benson Hill Biosystems	CRISPR <sup>a</sup>	2 codons altered
Maize	Northern Leaf Blight resistance	DuPont Pioneer	CRISPR	Allele replacement
Maize	Waxy starch	DuPont Pioneer	CRISPR	КО
Maize	Increased yield	Benson Hill Biosystems	Meganuclease	Allele replacement
Rice	Bacterial blight resistance	Iowa State University	TALEN	КО
Potato	Non-browing	Simplot Plant Sciences	TALEN	КО
Potato	Non-browing	Calyxt	TALEN	КО
Soybean	Drought tolerance	USDA-ARS	CRISPR	КО
Soybean	High oleic acid oil content	Calyxt	TALEN	КО
Тоbассо	Low nicotine	North Carolina State University	Meganuclease	КО
Wheat	Powdery mildew resistance	Calyxt	TALEN	КО
Wheat	High fiber <sup>a</sup>	Calyxt	TALEN	КО

USDA, FDA and EPA to update the Coordinated Framework. One of the three objectives was the need to ensure that the regulatory system is equipped to assess future products of biotechnology. Although the OSTP noted the need 'to prevent unnecessary barriers to future innovation and competitiveness', it never explicitly questioned whether products of biotechnology should be regulated even if no plausible hazards are identified. The same memo also requested that the National Academies of Sciences, Engineering, and Medicine (NASEM) write a report identifying future technologies and the regulatory issues they would raise (NASEM 2017). This report acknowledges that genome editing will play a prominent role in the future, but steers clear of making recommendations that single out the technology.

The USDA (2017b) responded to the challenge by taking advantage of its legal authority over noxious weeds to gain legal authority over edited plants. It proposed changing the definition of modification to 'techniques that use recombinant or synthetic nucleic acids with the intent to create or alter a genome' and declaring engineered and edited plants to be noxious weeds. Provisions were made to except plants, following agency review, in which the editing process either deleted DNA or just inserted one base pair at most.

On November 7, 2017, the USDA (2017c) withdrew its proposed rule-making following almost universal disapproval from both supporters and opponents of the technology. Therefore, the status quo prevails and, as announced on 28 March 2018 by the USDA Secretary (USDA 2018), there is no further intention to expand regulatory coverage. The statement reaffirms that if a change obtained through conventional means is not regulated, there is no reason to regulate the same change obtained using genome editing. At this point, even if a future administration would try to expand regulatory coverage to cover deletions obtained by genome editing, there may be too many edited products in the market by then to make their retroactive regulation feasible.

Nevertheless, whether or not the USDA is able to regulate edited plants, all plants used as food or feed fall under the purview of FDA, and if modified to resist diseases or pests, can also be regulated by the EPA (2001). Thus, lack of regulation by the USDA does not equate to lack of regulation in United States, as shown in Fig. 2.

### For FDA:

- Will crop be used for food or feed?
  - If yes → Regulated by FDA

### For EPA:

- Is the crop engineered to control or resist pests and pathogens?
  - If yes → Regulated by EPA

#### For USDA:

- Does the crop contain DNA from a pest or pathogen engineered in it?
  - If yes → Regulated by USDA
  - If no  $\rightarrow$  Was the DNA added with Agrobacterium?
    - If yes → Regulated by USDA
      - If no  $\rightarrow$  Is the crop a noxious weed?
        - If yes → Regulated by USDA

### The FDA position – the not-so-voluntary voluntary consultation

Plant-derived foods are the purview of the FDA's Center for Food Safety & Applied Nutrition. Historically, the FDA has been agnostic to the method of production, as long as the final product is safe, and has broad authority over food once it has reached the market place. If there is any doubt over a product's safety, it is possible to consult with the FDA prior to marketing a product. When it comes to crops, the FDA has a very broad definition for 'genetic modification', namely 'the alteration of the genotype of a plant using any technique, new or traditional' (FDA 1992). Historically, premarket consultation with FDA has never been required for plant varieties created with traditional breeding. In contrast, the FDA's voluntary consultation is perceived as a de facto requirement for plants created via rDNA. Against this backdrop, it is not totally clear where edited plants will fall. Responding to the OSTP, the FDA (2017a) requested public comments before formulating its policy on edited plants. As of yet, there has been no decision in response to the comments. One likely scenario is that the status quo will prevail, and that FDA will continue its not-so-voluntary premarket review of edited plants. The other scenario is that the FDA could follow USDA and not require any consultation. It is worth noting that as of this writing, the FDA is not listing consultations for edited crops on its page of official consultations (FDA 2018).

Another division of FDA, namely the Center for Veterinary Medicine (CVM), became responsible for edited animals. For its authority, CVM proposed to broaden the definition of a pharmaceutical (FDA 2017b) as that 'the portion of an animal's genome that has been intentionally altered whether mediated by rDNA or

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modern genome editing technologies is a drug because it is intended to alter the structure or function of the animal and thus, subject to regulation under our provisions for new animal drugs'. Because of the stringent pharmaceutical regulations, the review process will be prohibitively expensive for most edited animals as long as they are under the purview of FDA-CVM. If edited animals are ever to be commercially viable, either FDA-CVM will need to stop treating them like pharmaceuticals, or a different agency, such as the USDA, will need to oversee them.

#### The EPA position – the silent treatment

The EPA is the one agency that has remained completely silent on the topic of genome editing. Regardless, its regulatory authority is limited to pesticides, although it has stretched the definition of a pesticide as needed. Under current EPA regulations, what constitutes a 'pesticide' is defined by the intended purpose of the product, rather than by the intrinsic qualities of the product in question, meaning that, a pesticide is anything 'intended for preventing, destroying, repelling, or mitigating any pest'.

Thus, to be able to regulate plants engineered to resist insects or disease, the EPA invented a category of pesticides called plant-incorporated protectants (PIPs), defined as 'substances plants produce for protection against pests, and the genetic material necessary to produce these substances'. Plants edited for resistance thus far have lacked anything that could conceivably be called a PIP. Nevertheless, the edited plant itself could fall under the definition of pesticide.

It is also worth noting that whereas microorganisms engineered for pesticidal uses are covered under

**Fig. 2.** Flow chart of regulatory approvals needed in United States. Depending on the crop and trait, the resulting plant could be regulated by up to three different agencies.

FIFRA, microorganisms engineered for other purposes are classified as toxic substances under the Toxic Substances Control Act by the EPA. This latter category includes microalgae engineered for biofuel production. It is thus conceivable that edited microorganisms (e.g. for biofuel or bioremediation) could also be regulated by the EPA.

It is doubtful that the EPA will take any adverse position in the near future, given the prevailing anti-regulation sentiment of the current government in Washington. However, the EPA extended its PIP regulations to cover virus resistance in 2008 – 7 years after it invented PIPs – so current inaction is no predictor of future regulatory action.

# Labeling for foods from crops altered by rDNA

Labeling rules for crop-derived foods altered by rDNA will be announced in July 2018 (Public Law 2016). The USDA is in charge of the specific details through the Agricultural Marketing Service (AMS), and these are still pending as of this writing. To add to the general confusion, the definition of an engineered product that must be labeled is different from the definition of a product that must be regulated. The labeling definition also includes exemptions for modification that could have been obtained conventionally. Conceivably, this exemption should include many types of edited plants.

The AMS (2017) requested comments to guide its rule-making. The questions asked by the AMS hint that addressing the law's requirements will not be straight-forward:

- 1 Which breeding techniques should AMS as consider conventional breeding?
- 2 Which modifications should AMS consider to be found in nature?

A possible scenario is that plants with editing-induced deletions will not be labeled, while those with insertions or gene replacements may be. Any labeling requirement will be a strong disincentive for industry to use edited products, because of the cost of the sampling and detection assays needed to ensure the labels are truthful and compliant. And, regardless of what decision AMS makes as far as labeling, it will almost certainly be challenged in the courts, in which case a final decision could be delayed for an undefined period of time.

## Other considerations – the power of public opinion

Regardless of what regulations may be handed down by the Federal government, public opinion is the ultimate arbiter of acceptability. Case in point, non-GMO (Genetically Modified Organism) is the fastest growing sector of the food market at present, and the prediction over the next 4 years is that it will continue growing at 16% per year (Infiniti Research Limited 2017). Likewise, it is public acceptance that will likely dictate the potential for genome editing in American agriculture.

One of the main detractors to the use of genetic engineering in agriculture is the organic movement as the intentional use of genetically engineered materials was explicitly excluded when organic regulations were enacted in United States. This exclusion probably contributed to the public perception that genetic engineering in agriculture is not beneficial.

However, edited plants are not engineered plants, so the organic industry in United States has been moving to ensure edited plants are included in its exclusions. It has formulated the criterion that 'The genome is respected as an indivisible entity and technical/physical insertion, deletions, or rearrangements in the genome is refrained from (e.g. through transmission of isolated DNA, RNA, or proteins). In vitro nucleic acid techniques are considered to be invasion into the plant genome'. As such, any technology that invades the genome should therefore be an excluded method; this criterion clearly includes editing.

And, it is not just the organic industry that has expressed unease over genome editing. A major, mainstream industry group, in its comments to the FDA (2017c), states that it 'requests that FDA consider ways to [...] improve transparency and visibility to value chain stakeholders'. In other words, if editing is used, consumers need to know.

In summary, except for the USDA-APHIS, the US regulatory system for the products of biotechnology has not provided any clear guidance on the use of edited products in agriculture. Edited products, in which the edit is limited to deletions and does not contain any vector sequences that come from pest-derived DNA, will not be regulated, at least not in the near future, by the USDA. Such products probably will not need to be labeled either. Whether lack of immediate Federal oversight translates into greater or lesser public acceptance remains to be seen in the long term. Certainly, stringent Federal regulation of engineered crops over the past 20 years did not translate into general public acceptance.

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