Gene Editing in Agriculture – Regulatory Status and Legal Issues
Friday, November 8, 10:15am – 11:45am

1. Background on Regulation of Agricultural Biotechnology

    a. Governing principles derive from the Coordinated Framework for the Regulation of Biotechnology, issued by the White House Office of Science and Technology in 1986. 51 Fed. Reg. 23,302 (June 26, 1986).

    b. The drafters' effort was to "achieve a balance between regulation adequate to ensure health and environmental safety while maintaining sufficient regulatory flexibility to avoid impeding the growth of an infant industry." *Id*. at 23302-03.

    c. "While the recently developed methods are an extension of traditional manipulations that can produce similar or identical products, they enable more precise genetic modifications, and therefore hold the promise for exciting innovation and new areas of commercial opportunity." *Id.* at 23303.

    d. Products derived from biotechnology do not inherently pose any greater concern than traditional genetic modification approaches and in the U.S. safety assessments and regulatory reviews focus on the products of genetic modification, not the manner in which the modifications are achieved. *Id*. at 23,311-12, 23,338.

2. Regulatory oversight of the development and commercial use of these organisms was divided among three U.S. federal agencies—the United States Department of Agriculture ("USDA"), the Environmental Protection Agency ("EPA"), and the Food and Drug Administration ("FDA")—in a manner consistent with each agency's statutory and regulatory authority.

    a. "The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally fit within these agencies' review and approval regimens." 51 Fed. Reg. at 23304.

3. Plant Products of Gene Editing.

    a. USDA.

        i. USDA-APHIS-BRS assesses whether biotechnology-based plant products pose a plant pest risk. 7 C.F.R. § Part 340; https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions

        ii. Since at least 2011, USDA has utilized the "Am I Regulated?" process, under which a product developer can ask USDA in writing whether a particular organism is subject to the Agency's Part 340 regulations. https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated

        iii. The process has been in place since 2011 and has looked at over seventy (70) products, including numerous products produced using gene editing techniques.

Requests and responses are publicly available, subject to some withholding for confidential information. https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/regulated_article_letters_of_inquiry/regulated_article_letters_of_inquiry

iv. USDA has issued guidance on the Am I Regulated process. https://www.aphis.usda.gov/brs/pdf/AIR_Guidance.pdf

v. On June 6, 2019, USDA released for public comment a proposed revision to Part 340. 84 Fed. Reg. 26514 (June 6, 2019).

1. USDA had earlier proposed revisions to Part 340 in January 2017, 82 Fed. Reg. 7008 (Jan. 19, 2017), but ultimately withdrew that proposal, opting instead to take a "fresh look" at the issue and engage more broadly with stakeholders. https://www.usda.gov/media/press-releases/2017/11/06/usda-re-engage-stakeholders-revisions-biotechnology-regulations

2. In the interim, the Secretary of Agriculture released a statement addressing the Agency's planned approach to regulating products developed through new, innovative breeding techniques, like gene editing. https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation

3. That approach has largely been codified in the new proposal, which provides expanded opportunities for regulatory self-determination, a new, streamlined framework for assessing plant pest risk, and extensive provisions related to permitting, inspections, reporting, recordkeeping, and compliance. 84 Fed. Reg. 26514.

4. Key provisions include:

a. The regulations apply to GE organisms; while "GE organism" is not defined in the proposal, proposed Section 340.3 defines genetic engineering as "[t]echniques that use recombinant or synthetic nucleic acids to modify or create a genome."

b. Product developers whose plant products either (i) satisfy criteria derived from the Secretary's May 2018 statement, *e.g.*, are plants whose genetic modifications are "solely deletions of any size," or a "single base pair substation," among two others, or (ii) consist of a GE plant-trait-mode of action combination that has previously undergone a regulatory status review, described below, and found unlikely to pose a plant pest risk, may either self-determine, or may seek from the Agency a "confirmation," that "the plant is not within the scope" of Part 340. (§340.1) It is anticipated that many plant products of gene editing would be subject to the self-determination provisions of the proposed rule.

c. For GE plants not meeting the criteria identified in Section 340.1, a developer may (i) seek a permit from the Agency to enable the "movement" of such plant, with movement broadly defined to include release into the environment, and/or (ii) apply to the Agency for a "regulatory status review" (RSR), comprised of an Initial Review phase and, if needed, a more robust Plant Pest Risk Assessment (PPRA) (§340.2, 340.4), described more fully in a separate document accompanying the proposed rule. The RSR is aimed at assessing the potential for the GE plant, and specifically its plant-trait-mechanism of action combination, to pose a plant pest risk, defined as "the possibility of harm to plants resulting from introducing or disseminating a plant pest or exacerbating the impact of a plant pest." (§340.3)

d. Non-plant GE organisms subject to Part 340 are not eligible for self-determination under Section 340.1 or for the RSR process under Section 340.4, and may only be "moved" under permit. (§340.2)

e. Requests for and results of RSRs will be maintained on the Agency's website. (§340.4(c)). If an RSR proceeds to a PPRA, the results of the Agency's Initial Review and PPRA will be published in the Federal Register for public comment. Information regarding anticipated timelines for review of permits or RSR processes has not yet been provided.

f. Along with opportunities for self-determination and a streamlined approach to assessing plant pest risk, the Agency also proposes detailed provisions relating to permit application requirements, permit conditions, inspections, reporting, recordkeeping, and compliance, all of which stakeholders should review carefully. (§§340.5, and 340.6).

b. FDA.

i. FDA regulates human and animal food from genetically engineered plants like its regulates all food. FDA safety requirements impose a clear legal duty to market safe foods to consumers, regardless of the process by which such foods are created. It is unlawful to produce, process, store, ship or sell to consumers unsafe food. 21 U.S.C. § 321 *et seq*.; 21 U.S.C. § 342(a)(1).

ii. In 1992, FDA issued *Statement of Policy – Food Derived from New Plant Varieties*, 57 Fed. Reg. 22984 (May 29, 1992):

1. "Under this policy, foods, such as fruits, vegetables, grains, and their byproducts, derived from plant varieties developed by the new methods of genetic modification are regulated within the existing framework of the act, FDA's implementing regulations, and current practice, utilizing an approach identical in principle to that applied to foods developed by traditional plant breeding. The regulatory status of a food, irrespective of the method by which it is developed, is dependent upon objective

characteristics of the food and the intended use of the food (or its components). The method by which food is produced or developed may in some cases help to understand the safety or nutritional characteristics of the finished food. However, the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used." *Id*. at 22984-85.

iii. FDA created the Plant Biotechnology Consultation Program in the 1990s to work with genetically engineered plant developers to ensure that foods made with new plant varieties are safe and lawful. Under the voluntary consultation process, FDA evaluates the safety of foods before the enters the market.

iv. FDA completed its first biotechnology consultation in 1994. Consultations are publicly available. https://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon

v. In January 18, 2017, FDA issued a Request for Comments, seeking public comment about the safety of foods from genome edited plants, such as whether categories of genome edited plants present food safety risks different from other plants produced through traditional plant breeding. 82 Fed. Reg. 6564 (Jan. 19, 2017).

vi. In February 2019, FDA completed the biotechnology consultation process for a gene edited product, a soybean with increased levels of oleic acid and decreased levels of linoleic acid: https://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon&id=FAD2KO; *see also* https://www.fda.gov/media/120707/download

vii. FDA has indicated that it intends to issue draft guidance in 2019. https://www.fda.gov/safety/fdas-regulation-plant-and-animal-biotechnology-products/fdas-plant-and-animal-biotechnology-innovation-action-plan

c. EPA.

i. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

1. EPA regulates plant products of biotechnology under FIFRA where a plant has been engineered to demonstrate pesticide properties, e.g., a plant that is genetically modified to resist disease. 40 C.F.R. § Part 174.

ii. Toxic Substances Control Act (TSCA).

1. EPA regulates the use of intergeneric microorganisms, formed from organisms in different genera or those microorganisms formed with synthetic DNA not from the same genus, in commerce or commercial research. 62 Fed. Reg. 17910 (Apr. 11, 1997).

2. EPA's Office of Pollution Prevention and Toxics (OPPT) Biotechnology Program conducts a screening program for new microorganisms under section 5 of TSCA.

4. Animal Products of Gene Editing.

a. FDA regulates GE animals under the "new animal drug" provisions of the Federal Food, Drug and Cosmetic Act. 21 U.S.C. § 360b.

i. FFDCA Section 321(g) defines drugs to include, among other things, "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(C) (emphasis added). A "new animal drug" is:

1. [A]ny drug intended for use for animals other than man … (1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; … or … (2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions. 21 U.S.C. § 321(v).

ii. FDA has determined that when genetic material, like rDNA, is used to engineer an animal in a way that is intended to affect the structure or function of that animal, the rDNA construct meets the definitions of "drug" and "new animal drug." 21 U.S.C. §§ 321(g), (v).

iii. By law, an unapproved new animal drug is "unsafe" and, as a result, the drug itself and any food derived from the use of such a drug are "adulterated" and their marketing per se unlawful. 21 U.S.C. §§ 360b(a)(1), 342(a)(2)(C)(ii), 351(a), and 331.

iv. A new animal drug is approved—and thus lawful—when FDA finds that the developer, through the submission of controlled investigations, data, and other information, has proved that its product is both "safe" and "effective," i.e., that the rDNA construct is safe for the animal, that foods derived from the animal are safe, and that the rDNA construct works as intended. 21 U.S.C. § 360b(b)(1).

v. In 2009, FDA released guidance document entitled "Guidance for Industry 187: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs" ("Guidance 187"). The guidance discussed at length FDA's interpretation of the FFDCA and the attending regulatory process for GE animals and the approach it uses in reviewing the data and information submitted by a GE animal technology developer in support of the developer's New Animal Drug Application to make a risk-based evaluation of potential hazards and likelihood of harm.

vi. In 2015, FDA has approved one NADA in accordance with this process. https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/aquadvantage-salmon It remains the only approval to date.

b. On January 19, 2017, the FDA released for public comment draft revised Guidance for Industry (GFI) #187, "Regulation of Intentionally Altered Genomic DNA in Animals." 82 Fed. Reg. 6561 (Jan. 19, 2017).

    i. Revised Guidance 187 expanded the scope of the existing GFI #187 to address animals with intentionally altered genomic DNA developed through use of genome editing technologies, as well as techniques such as rDNA in genetic engineering.