Excerpted from

THE FAILURE OF FEDERAL BIOTECHNOLOGY REGULATION

*Alison Peck**

Abstract

The recent court case and state ballot measures regarding mandatory labels for GMOs suggest the need for a deeper conversation about the federal framework for regulating biotechnology. What is it about GMOs that consumers feel they have the "right to know"? Why has a generation of federal biotechnology regulation failed to satisfy consumer concerns? Are those concerns irrational, or is the regulatory structure inadequate? This Article argues that many consumer concerns underlying the labeling movement raise important scientific and extra-scientific questions that have been apparent since the advent of the technology in the 1980s. Moreover, these concerns persist because the Coordinated Framework for Regulation of Biotechnology has failed to respond to them effectively. The Coordinated Framework was based on statutes that pre-existed the technology and thus poorly fit the unique risks of genetic engineering. Today, genetic engineering is on the verge of a radical shift in technology, a shift that has already begun to burst the seams of those old statutes, leaving agencies with no regulatory authority at all over new products. This Article reviews the evidence behind persistent concerns about GMOs, considers the failures of the Coordinated Framework to address the most valid of those concerns, and canvasses policy questions that Congress must consider to more effectively tailor agency authority to address the risks and to enhance the potential of this rapidly-changing field of technology.

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II. THE FAILURE OF THE COORDINATED FRAMEWORK

On July 2, 2015, President Obama created an inter-agency task force among USDA, FDA, and EPA to update the Coordinated Framework for Regulation of Biotechnology[1] and develop a strategy to prepare for changes in biotechnology.[2] From the President's charge, it is not clear whether the work of the task force will be limited to adjusting federal regulatory authority based on current statutes (PPA, FDCA, and FIFRA), or whether the task force is also authorized to request that pass new legislation to expand or change federal agency statutory authority. The memorandum identifies the one-year objectives of the task force as "development of an updated [Coordinated Framework] to clarify the roles and responsibilities of the agencies that regulate the products of biotechnology," as well as the formulation of a long-term risk assessment strategy and the commissioning of an independent analysis of future biotechnology products.[3]

~~The federal review raises two important questions: First, to~~To what extent can and will the federal agencies reinterpret the scope of their existing authority under the relevant statutes in a way that addresses persistent consumer concerns? ~~And second, a~~Are those statutes sufficiently broad to allow the agencies to exercise jurisdiction in a way that meaningfully responds to concern concerns? This Part addresses failures of the Coordinated Framework to address consumer concerns – failures arising both from agency interpretation of existing authority and from lack of agency authority to regulate current and emerging products or ancillary impacts of those products.

A. Statutory Bases for Agency Jurisdiction under the Coordinated Framework

In the Coordinated Framework, the White House Office of Science and Technology Policy ("OSTP") divided regulatory authority for agricultural biotechnology among three federal agencies: the United States Department of Agriculture ("USDA"), which regulates the testing and commercialization of new

[1] Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986).

[2] Memorandum from the Executive Office of the President to Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture, July 2, 2015, *available at* https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf [hereinafter Coordinated Framework Executive Memorandum].

[3] *Id*. at 3.

agricultural biotech products; the Food and Drug Administration ("FDA"), which regulates the introduction and marketing of foods created through the use of genetic engineering; and the Environmental Protection Agency ("EPA"), which regulates genetically-altered microorganisms and pesticide properties of genetically-engineered plant varieties.[4] Each of these agencies regulates under statutes that pre-date commercial agricultural biotechnology. The Coordinated Framework located FDA's authority primarily in the Federal Food, Drug and Cosmetic Act ("FDCA"),[5] a 1938 act that includes authorization for the FDA to ensure food safety through regulation of food additives and misbranding.[6] The USDA's authority was identified as stemming primarily from a law that dates back to the Federal Plant Pest Act of 1957, reorganized in the Plant Protection Act ("PPA"), which gave the USDA jurisdiction over bacteria and viruses.[7] The Coordinated Framework identified EPA's authority as deriving from the relatively modern pesticide and toxics control laws of the 1970s, including the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA") and the Toxic Substances Control Act ("TSCA").[8]

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B. Insufficient Statutory Authority for USDA

The first generation of biotechnology typically used *Agrobacterium* as a vector to insert the DNA of one species into the cells of a different species.[9] Thus, the Office of Science and Technology Policy could argue that USDA's authority over plant pests also gave it authority over agricultural products created using these bacterial vector insertions of DNA (even though the viruses, once inserted, were not active and did not pose the types of threats

[4] *See* 1986 Coordinated Framework, *supra* note 16, at 23,302; *see also* Proposal for a Coordinated Framework for Regulation of Biotechnology, 49 Fed. Reg. 50,856 (Dec. 31, 1984) [hereinafter Proposed Coordinated Framework].

[5] Ch. 675, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301-399f (2012)).

[6] *See* 21 U.S.C. §§321(s) (defining "food additive"), 321(n) (defining "misbranding"), 331 (prohibiting introduction of adulterated or misbranded foods); 371-72 (providing for regulatory and enforcement authority by FDA).

[7] *See generally* 7 U.S.C. §§ 7701-7786 (2012).

[8] Ch. 125, 61 Stat. 163 (1947) (codified as amended at 7 U.S.C. §§ 136-136y (2012)). Congress originally enacted FIFRA in 1947; the act was rewritten in 1972. *Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)*, U.S. ENVTL. PROTECTION AGENCY, http://www.epa.gov/oecaagct/lfra.html (last updated June 27, 2012); ;Pub. L. No. 94-469, 90 Stat. 2003 (1976) (codified as amended in scattered sections of 15 U.S.C. (2012)); *See* Statement of Policy; Microbial Products Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act, 51 Fed. Reg. 23,313 (June 26, 1986) (providing the EPA policy statement for exercising authority under FIFRA and TSCA).

[9] *See* National Academy of Sciences, Genetically Engineered Crops: Experiences and Prospects 44-45 (2016).

that motivated the PPA).[10] As long as developers used bacterial or viral vectors to deliver DNA to target organisms, however, the PPA arguably provided an adequate jurisdictional hook. But biotechnology developers now have tools other than viruses at their disposal to make genetic modifications to target organism DNA. These tools include a "gene gun" that shoots DNA into cells without the use of any bacterial or viral vector, and genome-editing technologies that allow scientists to directly edit or delete DNA rather than inserting anything. Biotechnology now, in 2016, stands on the verge of a technological revolution that will allow scientists to edit genes easily and with minimal cost.

That technological revolution is based on changes in the mechanisms scientists use to accomplish genetic changes in an organism. When the Coordinated Framework was released in 1986, all GE plants had been produced by using *Agrobacterium tumefaciens* as the vector to deliver the DNA to the species of interest.[11] The administration's decision in the Coordinated Framework to locate FDA, USDA and EPA statutory authority in the FDCA, PPA, and FIFRA was based on the assumption that bacteria would continue to be the mechanism for accomplishing the genetic modifications.[12] Tellingly, however, the Coordinated Framework was out of date nearly as soon as it was written: Within months, scientists began to publicize successful inventions of genetically engineered plants through a process called particle bombardment, or the "gene gun."[13] Using a gene gun, scientists can coat microparticles with RNA or DNA and accelerate or shoot the particles to pierce cell walls of the plant. The resultant organism expresses the inserted genetic codes.[14] Since no plant pest is

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[10] *See* Alex Camacho et al., *Genetically Engineered Crops that Fly Under the US Regulatory Radar*, 32 NATURE BIOTECHNOLOGY 1087, 1088-89 (2014). In the Plant Protection Act, Congress found that "the detection, control, eradication, suppression, prevention, or retardation of the spread of plant pests or noxious weeds is necessary for the protection of the agriculture, environment, and economy of the United States." 7 U.S.C. § 7701. A "plant pest" is defined as "any living stage of any of the following that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product: (A) A protozoan. (B) A nonhuman animal. (C) A parasitic plant. (D) A bacterium. (E) A fungus. (F) A virus or viroid. (G) An infectious agent or other pathogen. (H) Any article similar to or allied with any of the articles specified in the preceding subparagraphs." 7 U.S.C. § 7702(14). In the case of a GMO, unlike the traditional "plant pest," the potential damage or disease to the plant is not caused directly by the *Agrobacterium* used to insert the new DNA, but by any unintended consequences of the resulting genetic modification.

[11] *See* National Academy of Sciences, *supra* note 9, at 331.

[12] *See* 1986 Coordinated Framework, *supra* note 16, at 23,302.

[13] *See* T.M. Klein et al., *High-velocity Microprojectiles for Delivering Nucleic Acids into Living Cells*, 327 NATURE 70 (1987).

[14] *Id*.

involved, APHIS's jurisdiction under the PPA is not triggered.[15] Another type of product already in use are null segregants, in which a transgenic parental line and a nontransgenic elite line are cross to produce nontransgenic progeny; the final product does not include the material used to transfer the new DNA, and thus does not trigger APHIS jurisdiction.[16]

Even more critical, new technologies or technologies now on the horizon that do not rely on plant pests will make direct genome editing fast, easy, and cheap.[17] Genome editing, an important class of new technologies, uses nucleases directed to a specific site on the DNA strand to delete, add, or change targeted DNA sequences in an organism.[18] Developers have used several different classes of these nucleases, most of which are best known by their space age-sounding acronyms: ZFNs, TALENs, and CRISPR.[19]

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CRISPR, the most promising of these techniques, accomplishes genetic mutations using two molecules – the Cas9 nuclease, which cuts both strands of DNA at a specific location to allow the mutation, and the guide RNA, a sequence of about twenty base pairs that guides Cas9 to the target location of the genome modification.[20] The breaks in DNA are repaired by the cell, leading

[15] *See, e.g.*, Letter from Michael C. Gregoire, Deputy Adm'r, Animal & Plant Health Inspection Serv., to Dr. Richard Shank, Senior Vice President, The Scotts Miracle-Gro Co. (July 1, 2011), *available at* http://www.aphis.usda.gov/brs/aphisdocs/scotts_kbg_resp.pdf ("Because no plant pests, unclassified organisms, or organisms whose classification is unknown were used to genetically engineer this variety of GE Kentucky bluegrass, APHIS has no reason to believe it is a plant pest and therefore does not consider the Kentucky bluegrass described in the letter dated September 13, 2010 to be regulated under 7 CFR part 340 and is not subject to the plant pest provisions of the PPA.").

[16] Camacho, *supra* note 10, at 1088.

[17] *See* Amy Maxmen, *Easy DNA Editing Will Remake the World. Buckle Up.*, WIRED (August 2015).

[18] *See* National Academy of Sciences, *supra* note 9, at 241; Nicholas J. Baltes & Daniel F. Voytas, *Enabling Plant Synthetic Biology Through Genome Engineering*, 33 Trends in Biotech. 120 (2015).

[19] *See* Thorben Sprink et al., *Plant Genome Editing by Novel Tools: TALEN and Other Sequence Specific Nucleases*, 32 Current Opinion in Biotech. 47 (2015) (describing use of meganucleases, ZFNs, and TALENs).; National Academy of Sciences, *supra* note 9, at 242.

[20] *See* Baltes & Voytas, *supra* note 18, at 123-24. For a simple layman's description of CRISPR/Cas9, see What Is CRISPR-Cas9, http://www.yourgenome.org/facts/what-is-crispr-cas9. *See also*; Khaoula Belhaj et al., *Editing Plant Genomes with CRISPR/Cas9*, 32 CURRENT OPINION IN BIOTECH. 76 (2015); Luisa Bortesi & Rainer Fischr, *The CRISPR/Cas9 System for Plant Genome Editing and Beyond*, 33 BIOTECH. ADVANCES 41 (2015); S. Antony Ceasar et al., *Insert, Remove, Replace: A Highly Advanced Genome Editing System Using CRISPR/Cas9*, BIOCHIMICA ET BIOPHYSICA ACTA (BBA) – MOLECULAR CELL RES. (online June 24, 2016),

to deletions, insertions or rearrangements using the template RNA sequence.[21] The CRISPR/Cas9 system, which was based on the discovery of a similar natural system in some bacteria to resist viruses, is simple and cheap to use because it only requires scientists to synthesize the short, twenty-nucleotide RNA sequence.[22]

Applications for genome editing using site-specific nucleases, especially CRISPR/Cas9, are promising for both human and animal welfare.[23] In agriculture, for example, researchers are working to introduce into dairy cattle a genetic variant that causes into some beef cattle to lack horns.[24] Farmers often de-horn dairy cattle, which are kept in close quarters, for safety reasons but physical de-horning methods are invasive, painful, and expensive.[25] To introduce the trait through traditional cross-breeding would result in loss of favorable traits for dairy production, but genome editing could introduce the variant into existing dairy herds without interfering with other, desirable traits.[26] In medicine, genome editing is being used to explore the possibility of knocking out the gene for CCR5, the functional co-receptor in T cells used by the HIV-1 virus.[27] People who naturally lack the CCR5 gene may become infected with the virus but do not become sick because their T-cells are resistant to being killed.[28] Knocking out the CCR5 gene in bone marrow stem cells might provide long-term HIV-resistant T cells to the recipient.[29]

The challenge of these technologies for USDA jurisdiction is that they do not rely on bacterial or viral vectors to accomplish the desired genetic modification. Without some form of plant pest

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http://www.sciencedirect.com/science/article/pii/S0167488916301781; National Academy of Science, *supra* note __, at 244.

[21] *See* Belhaj, *supra* note 20, at 76.

[22] *See* Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 Science 816 (Aug. 17, 2012); Ruud Jansen et al., *Identification of Genes that Are Associated with DNA Repeats in Prokaryotes*, 43 MOLECULAR MICROBIOLOGY 1565 (2002); Belhaj, *supra* note 20, at 76, 84.

[23] *See* Dana Caroll & R. Alta Charo, *The Societal Opportunities and Challenges of Genome Editing*, 16 GENOME BIOLOGY 242 (2015).

[24] *See* Wenfang Tan et al., *Efficient Nonmeiotic Allele Introgression in Livestock Using Custom Endonucleases*, 110 PROCEEDINGS OF NAT'L ACADEMY SCI. 16526 (2013); Wenfang (Spring) Tan et al., *Precision Editing of Large Animal Genomes*, 80 Advances in Genetics 37, 70-72 (2012).

[25] *See* Bruno Graf & Markus Senn, *Behavioral and Physiological Responses of Calves to Dehorning by Heat Cauterisation with or without Local Anasthesia*, 62 APPLIED ANIMAL BEHAVIOUR SCI. 153 (1999).

[26] *See* Dana Carroll & R. Alta Charo, *The Societal Opportunities and Challenges of Genome Editing*, 16 GENOME BIO. 242, 243 (2015).

[27] *See* Pablo Tebas et al., *Gene Editing of* CCR5 *in Autologous CD4 T Cells of Persons Infected with HIV*, 370 NEW ENGLAND J. MED. 901 (2014).

[28] *See* Carroll & Charo, *supra* note 26, at 245.

[29] *Id*.

present in the new product, APHIS has no grounds to exercise jurisdiction under the Plant Protection Act. Since no general statute gives APHIS jurisdiction over any form of biotechnology as such (a more adaptable type of process-based approach to regulation), nor over any new plant variety presenting novel risks (a product-based approach to regulation), APHIS cannot regulate or will not be able to regulate most new plant varieties created using biolistics, site-directed nucleases like ZFNs, TALENs, and CRISPR, and any other new methods that don't incorporate plant pests into the product organism.

This gap in APHIS oversight already exists and is expected to explode in the near future as CRISPR technology advance. Between 2011 and 2015, developers submitted letters of inquiry to APHIS regarding novel products, seeking to know whether the products would be regulated.[30] Of the forty-nine products for which letters of inquiry were submitted to APHIS, only four were determined by APHIS to involve plant pests that would give APHIS jurisdiction.[31] APHIS has indicated lack of regulatory jurisdiction over products created using biolistics (18), meganuclease deletions or substitutions (3), ZFNs (2), and TALENs (5).[32] Smaller laboratories and public institutions may already be deploying these technologies as a strategy for avoiding federal regulation.[33] Because CRISPR is simple and inexpensive, the technology may soon give rise to an explosion of new genetically engineered organisms from even very small research laboratories.[34]

The failure to capture new genome-editing technologies in federal regulatory authority may have safety consequences. Although these technologies offer important advancements over transgenic modifications because of their specificity and ability to limit off-target effects, techniques like CRISPR are not without risk that off-target effects will occur.[35] Without regulatory oversight,

[30] Developers may seek a confirmation of regulatory status from APHIS's Biotechnology Regulatory Services to determine whether their product is subject to the agency's oversight. *See* Animal and Plant Health Inspections Service, USDA, Am I Regulated Under 7 CFR part 340, https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated.

[31] *See* National Academies of Science, Engineering and Medicine, Genetically Engineered Crops: Experiences and Prospects 330 (2016) (Table 9-3); *see also* Camacho *supra* note 10, at 1090.

[32] *See* National Academy of Sciences, *supra* note 9, at 330 (Table 9-3).

[33] *See* Camacho, *supra* note 10, at 1087.

[34] *See* Amy Maxmen, *Easy DNA Editing Will Remake the World. Buckle Up.*, WIRED (August 2015).

[35] *See* Heidi Ledford, *Enzyme Tweak Boosts Precision of CRISPR Genome Edits*, Nautre (Jan. 6, 2016), http://www.nature.com/news/enzyme-tweak-boosts-precision-of-crispr-genome-edits-1.19114; *cf.* Benjamin P. Kleinstiver et al., *High-Fidelity CRISPR-Cas9 Nucleases with No Detectable Genome-Wide Off-Target Effects*, 529 Nature 490 (Jan. 28, 2016); Yangfang Fu et al., *Improving*

unintended consequences may occur and introduce risks that are not known until after commercialization and widespread release of the organism.

At the same time, other new genetic engineering technologies raise the possibility of *too much* regulation. These new products of genetic engineering may not raise the same level of risk, or generate the same level of public concern, as traditional transgenic products, but might nevertheless be subject to the same level of oversight under the PPA if accomplished using bacterial vectors. For example, J.R. Simplot has developed a variety of potato using a technique known as intragenesis.[36] In intragenesis, developers package various plant DNAs from varieties of the target crop or its sexually compatible relatives, combine them into a gene delivery cassette, and insert them into the target organism.[37] Unlike transgenic organisms, which combine DNA from non-sexually-compatible species, these intragenic organisms could be made through conventional breeding, just less efficiently.[38] While intragenic organisms may use *Agrobacterium*-mediated transformation and thus trigger APHIS's jurisdiction under the PPA, the use of cisgenesis has trigger debate about whether these organisms pose the same level of risk as transgenic organisms and whether they should be regulated the same.[39]

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C. Insufficient Statutory Authority for FDA

Like USDA's authority under the PPA, the Reagan Administraiton's decision to locate FDA's statutory authority in the FDCA was also based on the assumption that genetic engineering involved transgenic organisms.[40] FDA's jurisdiction over GMO

CRISPR-Cas Nuclease Specificity Using Truncated Guide RNAs, 32 NATURE BIOTECH. 279 (2014) (describing advances in substantially limiting off-target effects of CRISPR/Cas9 genome editing).

[36] *See* Ingrid Baekstad Holme et al., *Intragenesis and Cisgenesis as Alternatives to Transgenic Crop Development*, 11 PLANT BIOTECHNOLOGY J. 395, 395 (2013).

[37] *See* National Academy of Science, *supra* note 9, at 37.

[38] *Id*.

[39] *See* Henk J. Schouten et al., *Cisgenic Plants Are Similar to Traditionally Bred Plants: International Regulations for Genetically Modified Organisms Should Be Altered to Exempt Cisgenesis*, 7 EMBO REP. 750 (2006) (arguing that regulation is unnecessary because cisgenic organisms do not contain genes that they could not be crossed with in nature), *but see* Eva Sirinathsinghji, Cisgenesis is still genetic modification with all the attendant risks, Institue of Science in Society, http://www.i-sis.org.uk/Cisgenesis_is_still_Genetic_Engineering_with_all_attendant_risks.php (arguing that cisgenics should be regulated similarly to transgenics because all processes of genetic engineering introduce same risks of changes to target protein or off-target effects regardless of sexual compatibility of DNA sources).

[40] *Cf.* Coordinated Framework, 51 Fed. Reg. at 23,302-23,304; *see also* FDA, Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg.

foods derives from the FDCA, which allows FDA to regulate "food additives."[41] Since the first genetically-engineered foods involved the insertion of new DNA into a plant's genome using bacterial vectors, that generation of GMO foods arguably fell within the statutory definition of a food additive, "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food."[42]

If FDA had chosen to require new GE foods to go through pre-market safety review as food additives, regulatory oversight and public participation would be significant. Under full pre-market safety review for food additives, food producers are required to submit a petition to FDA demonstrating safety of the food, accompanied by supporting data generated by scientifically accepted methods.[43] FDA may also require the petitioner submit samples of the additive for testing, and provide descriptions of production methods and facilities.[44] FDA is required to make an independent determination within ninety days as to the safety of the food before the food can be marketed.[45] The regulation to approve the additive proposed by the petitioner must be published within thirty days of filing; although the FDCA does not mandate pre-order notice and comment, FDA as a practical matter receives or invites public comment on the proposed regulation.[46] Orders issued by the FDA may be stayed pending a challenge by any person adversely affected and are subject to judicial review.[47]

In a 1992 policy statement, however, FDA announced a presumption that all GE foods are safe and thus exempt from food additive pre-market safety review process.[48] A "food additive," as defined in the statute, includes substances described above only "if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe

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23,312-23,313 (June 26, 1986) (basing discussion of statutory jurisdiction on genetic engineering using recombinant DNA techniques).

41 21 U.S.C. § 348.

42 21 U.S.C. § 321(s).

43 21 U.S.C. § 348(b)(2).

44 *Id*. § 348(b)(3)-(4).

45 *Id*. § 348(c)(1)-(3) ("No evaluation shall issue if a fair evaluation of the data before the Secretary – (A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe.")

46 *Id*. § 348(b)(5); *See* Lars Noah & Richard A. Merrill, *Starting from Scratch?: Reinventing the Food Additive Approval Process*, 78 BOSTON UNIV. L. REV. 329, 371 (1998).

47 21 U.S.C. § 348(e)-(f), § 348(g)

48 *See* FDA, Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (May 29,1992) [hereinafter FDA Statement of Policy].

under the conditions of its intended use . . . "[49] According to FDA, all foods derived from genetic engineering fall into this GRAS ("generally recognized as safe") exemption from the pre-market safety review process.[50] FDA reasoned, that "transferred genetic material [nucleic acids] . . . are present in the cells of every living organism . . . and do not raise a safety concern as a component of food. In regulatory terms, such material is presumed to be GRAS."[51]

As a result of this presumption, all foods produced using genetic engineering are exempt from the pre-market safety review process for food additives unless FDA the intended expression of the genetic material differs significantly from substances already found in food.[52] Subsequent litigation showed that this presumption was questioned even by scientists within FDA at the time it was announced.[53] FDA's GRAS presumption and its consequences also raise democratic concerns: Without pre-market safety review, no public record of FDA food safety approvals is created, and the public is deprived of any opportunity to review or comment on those decisions. Given the scientific uncertainty about the health effects of consuming GMOs, this lack of transparency has led to considerable consumer distrust of FDA's determinations. FDA encourages a voluntary, non-public consultation process, which as a matter of practice all developers have utilized before bringing a new GMO food to market.[54]

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[49] 21 U.S.C. § 321(s).

[50] FDA Statement of Policy at 22,990.

[51] *Id*.

[52] *Id*.

[53] FDA produced documents containing statements by its scientists critical of FDA's GRAS presumption in discovery in a lawsuit over FDA labeling policy, Alliance for Biointegrity v. Shalala, 116 F. Supp. 2d 166 (D.D.C. 2000). *See, e.g.*, Memorandum from Edwin J. Matthews, Department of Health and Human Services, to Toxicology Section of the Biotechnology Working Group (Oct. 28, 1991) ("a genetically engineered plant may contain an identical profile of expected plant toxicant levels… as is normally found in a closely related, natural plant. However, genetically modified plants could also contain unexpected[ly] high concentrations of plant toxicants"); Memorandum from Dr. Louis J. Pribyl on Biotechnology Draft Document 1 (March 6, 1992) ("There is a profound difference between the types of unexpected effects from traditional breeding and genetic engineering which is just glanced over in this document."). Those documents are available on Alliance for Biointegrity's website, http://www.biointegrity.org.

[54] *See* FDA, Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984, 22,991 (May 29, 1992); *see also* Consultation Procedures under FDA's 1992 Statement of Policy – Foods Derived from New Plant Varieties (June 1996, rev. Oct. 1997), *available at* http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm096126.htm; In 2001, FDA proposed making the premarket consultation requirement mandatory, *see* FDA, Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. 4706 (2001), but the rule was never made

Moreover, it is unclear whether foods produced with new genetic engineering technologies will even fall within the FDCA definition of "food additive," which applies only to substances that "becom[e] a component or otherwise affect[] the characteristics of any food."[55] In its 1992 policy statement, FDA stated, "[i]n the case of foods derived from new plant varieties, it is *the transferred genetic material* and the intended expression product or products that could be subject to food additive regulation, if such material or expression products are not GRAS."[56] But new genetic engineering techniques do not necessarily involve transferring any material into the plant products at all: genome editing techniques like CRISPR, for example, directly edit the genome of the target organism without inserting any new material.

The "food additive" definition is deliberately broad, encompassing not only substances that become final components of the food but also substances used in production, manufacturing, and other phases of the food supply chain, if those substances are intended to affect the characteristics of the food.[57] Nevertheless, the definition clearly hinges on the existence of a "substance." Under longstanding federal biotechnology policy, however, a genetic engineering *process* is differentiated from the genetic engineering *product*.[58] As long as FDA adheres to this policy choice, it will be difficult to stretch the definition of "food additive" to accommodate foods produced through genetic engineering processes that do not involve the addition of any "substance" even in the production phase. Without the jurisdictional hook of food additive review under the FDCA, it is unclear whether FDA will have any jurisdiction over new genetically-engineered foods, even the current voluntary pre-market consultation process. Even FDA's authority to remove unsafe products from the market is based on its jurisdiction over "adulterated foods," which are defined as "substances" that render the food injurious to health.[59] The definition also excludes any substance that is "not an added substance . . . if the quantity of such substance in such food does not ordinarily render it injurious to

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final. *See* Proposed Rule, Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. at 4707-08.

55 21 U.S.C. § 321(s).

56 Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,990.

57 21 U.S.C. § 321(s).

58 *See* Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57 Fed. Reg. 6,753, 6,756 (Feb. 27, 1992) ("No conceptual distinction exists between genetic modification of plants and microorganism by classical methods or by molecular techniques that modify DNA and transfer genes.") (quoting National Research Council, Field Testing Genetically Modified Organisms: Framework for Decisions 14 (1989)).

59 21 U.S.C. § 321(a)(1).

health."[60] Genetically-engineered foods with no "added substance" may evade even FDA's recall authority even in the event of a verified health hazard.

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[60] *Id*.