FDA Regulation of Food from New Plant Varieties

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Office of Food Additive Safety
Does FDA regulate genome edited plants?

CRISPR-edited crops free to enter market, skip regulation

Emily Waltz

Nature Biotechnology 34, 562 (2016) | doi:10.1038/nbt.3316-562
Published online 09 June 2016

Gene-edited CRISPR mushroom escapes US regulation

A fungus engineered using CRISPR–Cas9 can be cultivated and sold without oversight.

BY EMILY WALTZ

The US Department of Agriculture (USDA) will not regulate a mushroom that has been genetically modified with the gene-editing tool CRISPR–Cas9, the agency has confirmed. The long-awaited decision means that the mushroom can be cultivated and sold without passing through the agency’s regulatory process—making it the first CRISPR-edited organism to receive a green light from the US government.

“The research community will be very happy with the news,” says Zanzia Gao, a plant biologist at the Chinese Academy of Sciences Institute of Genetics and Developmental Biology in Beijing, who was not involved in developing the mushroom. “I am confident we’ll see more gene-edited crops falling outside of regulatory authority.”

Yinong Yang, a plant pathologist at Pennsylvania State University (Penn State) in University Park, engineered the fungus—the common white button mushroom (Agaricus bisporus)—to resist browning. The effect is achieved by targeting the family of genes that encodes polyphenol oxidase (PPO), an enzyme that causes browning. By deleting just a handful of base pairs in the mushroom’s genome
Does FDA regulate genome edited plants?

- All food is regulated, regardless of how plant varieties are bred

- No unique requirements exist for food developed with biotechnology
  - Plant Biotechnology Consultation Program (voluntary)

- All food must meet universal regulatory requirements
  - All food must be safe
FD&C Act: Legal provisions for all food

- Federal Food Drug & Cosmetic Act (FD&C Act)
- Food from GE crops must meet the same legal requirements as other foods:

  - **Endogenous Substances**
    
    Food must be safe

  - **Additives**
    
    “Food additives” require premarket review and approval

  - **Labeling**
    
    Labeling must be truthful and not misleading
How the FD&C Act applies to food from GE plants
Levels of Endogenous Substances Must Be Safe

Endogenous Substances

Solanine (a glycoalkaloid)

> 200mg/kg glycoalkaloids

< 200 mg/kg glycoalkaloids
The FD&C Act applies to food from GE plants
Added Substances: Must Be “Generally Recognized as Safe” or Require FDA Review & Approval

FD&C Act

Added Substances

“Generally Recognized as Safe” (GRAS)
Legal without premarket approval
• Safe (reasonable certainty of no harm)
• Safety info publically available
• Safety info widely accepted by experts

“Food Additive”
Premarket review & approval required
• Safe (reasonable certainty of no harm)
• Safety info not yet publically available
• Safety info not yet widely accepted by experts

Glyphosate tolerant corn with CP4 EPSPS protein
Added Substances: Must Be “Generally Recognized as Safe” or Require FDA Review & Approval

FD&C Act

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Glyphosate tolerant corn with CP4 EPSPS protein
The FD&C Act applies to food from GE plants

Endogenous Substances  
Added Substances  
Labeling
Labeling Must Be Truthful and not Misleading

- Truthful and not Misleading
- Common or Usual Name
- Must Disclose "Material Facts"

GE Soybean with increased levels of oleic acid

New name: "High oleic soybean oil"

Oleic acid content in oil

- Typical soybean oil: 25%
- GE Soybean oil: 75%
- Olive oil: 72%

FDA
National Bioengineered Food Disclosure Standard (2016)

• Responsibility of USDA’s Agriculture Marketing Service (AMS)
  – July 2018

• Marketing, not safety
• Not in FDA’s purview
Consult with FDA to Ensure Compliance

FD&C Act

Endogenous Substances

Added Substances

Labeling

Consult with FDA

Resolve safety and regulatory questions before marketing

Ensure compliance
FDA’s Plant Biotechnology Consultation Program

• **Voluntary** program

• Checks for compliance with **mandatory** safety standards

• Developers of GE crops have routinely participated
  – FDA has evaluated over 150 GE plant lines
Consulting with FDA

- Early Consultation phase
- Developer submits safety and regulatory assessment
- FDA team of experts evaluates the data and information
- FDA requests additional information as needed
- Repeat until safety and regulatory questions are resolved
- FDA summarizes evaluation in a memo
- FDA ends consultation by sending a letter to the developer
Elements of a Submission

- Basic Information
- Endogenous Substances
- Added Substances
- Labeling

- The plant
- The foods
- The new trait
- The inserted DNA
  - Transformation method
  - Plasmid
  - Molecular characterization
  - Stability
Elements of a Submission

- Basic Information
- Endogenous Substances
  - The composition
    - Toxicants, anti-nutrients
    - Key nutrients
- Added Substances
- Labeling
Compositional Assessment

New variety
Toxicants
Anti-nutrients
Key nutrients

Appropriate comparator?
(Grown concurrently)
To characterize changes in composition

Data on other varieties
To understand existing variability

Information on other comparable foods?
To build safety narrative
Elements of a Submission

- **Basic Information**
- **Endogenous Substances**
- **Added Substances**
  - New proteins
    - Toxicity and allergenicity assessment
  - New metabolic pathways
    - Safety assessment
- **Labeling**
Elements of a Submission

- Basic Information
- Endogenous Substances
- Added Substances
- Labeling
  - Common or usual name
  - “Material” differences?
## Completed Consultations Posted on FDA’s Website

<table>
<thead>
<tr>
<th>BNF No.</th>
<th>Traits</th>
<th>Food</th>
<th>Event Designation Unique Identifier</th>
<th>FDA Letter Date (sorted Z-A)</th>
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<tbody>
<tr>
<td>156</td>
<td>Insect Resistance</td>
<td>Rice</td>
<td>Huahui No.1 HZU-HH001-0</td>
<td>Jan 9, 2018 (PDF, 37 kB)</td>
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<td>157</td>
<td>Male Sterility and Herbicide Tolerance</td>
<td>Canola</td>
<td>MS11 BCS-BN012-7</td>
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<td>155</td>
<td>Altered growth properties</td>
<td>Soybean</td>
<td>HB4 INO-003410-5</td>
<td>Aug 2, 2017 (PDF, 45 kB)</td>
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<td>153</td>
<td>Change in composition (other) and pest resistance</td>
<td>Potato</td>
<td>X17 SPS-00X17-5</td>
<td>Feb 21, 2017</td>
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<td>153</td>
<td>Change in composition (other) and pest resistance</td>
<td>Potato</td>
<td>Y9 SPS-00Y9-7</td>
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<tr>
<td>149</td>
<td>Change in Composition (other) resulting in Altered Color</td>
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<td>Event EF2-114 FDP-00114-5</td>
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<tr>
<td>151</td>
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<td>Corn</td>
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<td>148</td>
<td>Herbicide tolerance</td>
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<td>Altered Growth Properties</td>
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<td>Potato</td>
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</table>

100+ consultations completed

[www.fda.gov/bioconinventory](http://www.fda.gov/bioconinventory)
Completed Consultations

Crops (# of events)

- Corn (45)
- Potato (35)
- Soybean (19)
- Cotton (25)
- Canola (18)
- Other* (15)
- Tomato (7)
- Sugar beet (3)
- Alfalfa (3)
- Radicchio (3)

* Squash (2), cantaloupe (2), apple (2), rice (2), papaya (2), plum (1), flax (1), wheat (1), pineapple (1) creeping bentgrass (1)
Completed Consultations
Traits (# of events)

- Insect resistance (Bt)* (71)
- Herbicide tolerance (52)
- Virus resistance (RNAi)* (19)
- Male sterility (13)
- Reduced browning (9)
- Delayed ripening (8)
- Altered composition (8)
- Lower acrylamide potential (7)
- Processing enzymes (5)
- Increased yield (2)
- Drought tolerance (1)
- Insect resistance (RNAi)* (1)
- Disease resistance (R protein)* (1)

* Plant-incorporated protectants regulated by EPA
New Protein Consultations

• For proteins in GE crops early in development

• Potential unintended presence in food

• FDA issued guidance in 2006 to establish mechanism for FDA to evaluate new proteins before field testing

Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use
### Completed New Protein Consultations

<table>
<thead>
<tr>
<th>NPC Submission No. (sorted Z-A)</th>
<th>Protein</th>
<th>Developer</th>
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<th>Date of FDA’s Response Letter</th>
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<tr>
<td>18</td>
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<td>Agrivida, Inc.</td>
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<td>Feb 21, 2018 (227 kB)</td>
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<td>isopentenytransferase (IPT)</td>
<td>Arcadia Biosciences, Inc.</td>
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<td>14</td>
<td>trypsin</td>
<td>Applied Biotechnology Institute</td>
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<td>Sep 2, 2015</td>
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<td>12</td>
<td>5-enolpyruvate-3-phosphate synthase (EPSPS ACE)</td>
<td>Athenix Corporation</td>
<td>Oct 7, 2009 (PDF, 596 kB)</td>
<td>Oct 15, 2010</td>
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<td>10</td>
<td>p-hydroxyphenylpyruvate dioxygenase (HPPD)</td>
<td>Bayer CropScience LP</td>
<td>Jun 5, 2009 (PDF, 121 kB)</td>
<td>Mar 26, 2010 (withdrawn*)</td>
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<td>aryloxyalkanoate dioxygenase-12 (AAD-12)</td>
<td>Dow AgroSciences LLC</td>
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<td>May 18, 2010</td>
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<td>Dow AgroSciences LLC</td>
<td>Mar 28, 2007 (PDF, 27 kB)</td>
<td>Dec 22, 2009 (withdrawn*)</td>
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</table>
Engaging with FDA R&D Timeline

1. Lab & Greenhouse
   – Informal consultations
   – New Protein Consultation (NPC)

2. Pre-release
   – Informal consultations
   – Plant Biotechnology Consultation Program (BNF)

3. Commercialization
   – Ongoing legal responsibility to ensure safety and compliance
FDA & Genome Editing of Food Plants

National Strategy for Modernizing the Regulatory System for Biotechnology Products

Product of the Emerging Technologies Interagency Policy Coordination Committee’s Biotechnology Working Group

September 2016

“FDA intends to clarify its policy for the regulation of products derived from genome editing techniques, including, as appropriate, identifying and/or updating relevant existing guidance documents.”
FDA & Genome Editing of Food Plants

1. We are working on a policy on genome editing

2. We sought public input to help inform regulatory approach

Summarized questions:
- Is past experience relevant to genome-edited crops?
- Are there types of genome-edited crops that would be
  • less likely to raise different or greater risks?
  • more likely to raise different or greater risks?
  • If so, which ones?
- Are there ways we help small companies work with us?

3. We identified substantive responses out of the 582 received

4. We are considering substantive responses and are developing a course of action
Foods Derived From Plants Produced Using Genome Editing

Q: What is genome editing?

A: “Genome editing” is a term used to describe a relatively new set of technologies that enable one to make precise changes in the DNA of a plant, animal or other living organism. For example, such technologies can be used to introduce, remove, or substitute one or more specific nucleotides at a specific site in the organism’s genome. Genome editing is being performed using, for example, clustered regulatory interspersed short palindromic repeat associated nucleases (CRISPR), zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and oligonucleotide-directed mutagenesis (ODM).

Q: What is FDA doing in this area?

On January 18, 2017, FDA announced a Request for Comments (RFC) seeking public input to help inform its regulatory approach to human and animal foods derived from plants produced using genome editing. The RFC asks for data and information in response to questions 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.

Additionally, the agency is asking for information on how best to engage small businesses, including those that may be considering using genome editing to produce new plant varieties for use in human or animal food.

On April 13, 2017, the FDA extended the comment period for the Request for Comment. Comments should be submitted to the FDA by June 19, 2017 to ensure they are taken into consideration. Comments received will help inform FDA’s thinking on human and animal foods derived from new plant varieties produced using genome editing.

To comment on the RFC, go to Regulations.gov and insert docket number FDA-2016-N-4389. To submit comments to the docket by mail, use the following address. Be sure to include docket number FDA-2016-N-4389 on each page of your written comments.

Division of Dockets Management
HFA-365
Food and Drug Administration
5630 Fishers Lane, Room 1051
Rockville, MD 20852

Q: Why is the FDA requesting information from the public regarding crops used for human and animal food that have been produced through the use of genome editing?

A: In September 2016, OSTP issued a National Strategy for Modernizing the Regulatory System for Biotechnology
In-house, informal plant biotechnology R&D database

- Food crops
- Traits with potential commercial value
- Cannot judge whether developers intend to commercialize

**Sources:**
- All public
- Scientific literature
- Scientific conferences
- Company websites
- Media reports
- USDA “Am I Regulated” Letters

<table>
<thead>
<tr>
<th></th>
<th>Entries as of April 2017</th>
<th>Entries as of April 2018</th>
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</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>459</td>
<td>690</td>
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<tr>
<td><strong>Genome edited</strong></td>
<td>45</td>
<td>82</td>
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</table>
Genome editing R&D: Traits

Altered composition: Examples
- Altered oil composition (6)
- Altered starch (5)
- Low gluten

Other: Examples
- Non-browning
- Biofuels
- Drought tolerant
- Self-compatible
- Parthenocarpic
- Gynoecious
- Shatter resistant
- Low-cesium
- Delayed softening

Sources: Scientific literature, scientific conferences, company websites, media reports, USDA “Am I regulated?” Letters
Genome editing R&D: Crops

Sources: Scientific literature, scientific conferences, company websites, media reports, USDA “Am I regulated?” Letters
Genome editing R&D: Methods

- CRISPR: 55
- TALEN: 14
- Oligonucleotide-mediated Meganuclease: 5
- Zinc Finger: 1
- Other: 2

Sources: Scientific literature, scientific conferences, company websites, media reports, USDA “Am I regulated?” Letters
Genome editing R&D: Countries

Sources: Scientific literature, scientific conferences, company websites, media reports, USDA “Am I regulated?” Letters

China: 16
Japan: 5
Korea: 4
Germany: 3
France: 2
Italy: 3
Other: 10

USA: 48

Other: Australia, Israel, Kenya, Mexico, Philippines, Spain, Sweden, Switzerland, UK, Uruguay
Genome editing R&D: Developers

- Academic: 50
- Start-Ups: 18
- Established Companies: 11
- Other Organizations: 3

Sources: Scientific literature, scientific conferences, company websites, media reports, USDA “Am I regulated?” Letters
The Agricultural Biotechnology Education and Outreach Initiative

• Science-based educational information on agricultural biotechnology
  – Including environmental, nutritional, food safety, economic, and humanitarian aspects

• $3M appropriated by Congress

• FDA led, in collaboration with EPA, USDA
  – Over 60 people in the US Government involved

• Work ongoing
  – Public engagement phase complete
  – Now concluding research phase
    • Unprecedented effort
The Agricultural Biotechnology Education and Outreach Initiative

Agricultural Biotechnology Education and Outreach Initiative November 2017 Meetings

The U.S. Food and Drug Administration held public meetings in Charlotte, North Carolina, and San Francisco, California, regarding its Agricultural Biotechnology Education and Outreach Initiative. Congress appropriated $3 million to fund this initiative, which calls upon the FDA to work with USDA to provide education and outreach to the public on agricultural biotechnology and food and animal feed ingredients derived from biotechnology.

The purpose of the public meetings was to provide the public with an opportunity to share information, experiences, and suggestions to help inform the development of this education and outreach initiative.

Meeting Information & Materials

Charlotte, North Carolina

Tuesday, November 7, 2017, from 8:00 am to 1:00 pm EST
Omni Charlotte Hotel
132 E Trade Street
Charlotte, NC

Charlotte Meeting Agenda (PDF 50KB)
Charlotte Meeting Transcript (PDF 179KB)
Charlotte Meeting Recording
Recordings of meetings are publicly available
Public Comment on Outreach Initiative

• **Questions for public comment:**
  – What are the specific topics, questions, or other information that consumers would find most useful, and why?
  – Currently, how and from where do consumers most often receive information on this subject?
  – How can FDA (in coordination with USDA) best reach consumers with science-based educational information on this subject?

• **662 responses**
  – Publicly available
The Agricultural Biotechnology Education and Outreach Initiative

Agricultural Biotechnology Education and Outreach Initiative

Congress appropriated $2 million to fund the Agricultural Biotechnology Education and Outreach Initiative, which calls upon the FDA to work with USDA to provide education and outreach to the public on agricultural biotechnology and food and animal feed ingredients derived from biotechnology.

Plants, food, and food ingredients developed using genetic engineering were introduced into the U.S. food supply in the 1990s. Public and private sector scientists knowledgeable in genetic engineering, toxicology, chemistry, nutrition, and other scientific areas have carefully evaluated and assessed the safety of these products and have determined that such products are safe for human and animal consumption. The Committee provides a total of $2,000,000 for the FDA to coordinate with USDA to provide education and outreach to the public on the safety and benefits of crop biotechnology and food and animal feed ingredients derived from biotechnology. The Committee expects this educational information to be posted on both agency websites and through other social media and communications platforms within 60 days of enactment of this Act.

from H. Rept. 114-531 - AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS BILL, 2017

Initiative Goal

The goal of this initiative is to provide consumer outreach and education through publication and distribution of science-based educational information on the environmental, nutritional, food safety, economic, and humanitarian impacts of agricultural biotechnology. The FDA is currently working on this initiative in consultation with USDA and other federal agencies.

A steering committee and four workgroups have been set up to coordinate all the work for this initiative.

Initial Phase

The initial phase of this initiative was to inform the public of our work and obtain input from all stakeholders on this issue. The FDA held two public meetings in November 2017 and opened a docket to receive public comments.

In addition, FDA initiated work to examine the latest science and research studies relevant to consumer education and outreach to help inform the development of educational materials for this initiative.

Current Efforts
Thank You

- **FDA’s Plant Biotechnology Consultation Program**
  - [www.fda.gov/GEPlantFoods](http://www.fda.gov/GEPlantFoods)
  - Food from GE Plants
  - How FDA regulates Food from GE Plants
  - Q&As
  - Links to guidance and policy documents

- **Listing of all completed consultations**
  - [www.fda.gov/bioconinventory](http://www.fda.gov/bioconinventory)
  - Documents from completed consultations