FDA Regulation of Food from New Plant Varieties: An Overview

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Office of Food Additive Safety
Overview

• FDA’s regulatory approach:
  – Regulatory authorities related to food from GE plants

• How to consult with us:
  – The types of data and information FDA evaluates

• Past consultations

• New Protein Consultations
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:

  - **General Safety**
    
    Food must be safe. Applies to endogenous substances (post-market authority)

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

  - **Labeling**
    
    Labeling must be truthful and not misleading
FDA’s Statement of Policy (1992)
Foods Derived from New Plant Varieties

• Addressed **new plant varieties**
  – Including recombinant DNA (rDNA) technology

• Identified potential safety considerations

• Identified applicable legal requirements and concluded that the existing legal framework is sufficient to ensure safety

• Proposed considerations for ensuring safety and compliance before marketing
How the FD&C Act applies to food from GE plants

- **Endogenous Substances**
- **Added Substances**
- **Labeling**
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

FD&C Act

Endogenous Substances

Added Substances

Labeling
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

Glyphosate
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
Labeling Must Be Truthful and not Misleading

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

New name: “High oleic soybean oil”

Oleic acid content in oil

- Typical soybean oil: 25%
- GE Soybean oil: 75%
- Olive oil: 72%
National Bioengineered Food Disclosure Standard (2016)

- Responsibility of USDA’s Agriculture Marketing Service (AMS)
- Marketing (not safety related)
- 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
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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
  - Human and animal
- The new trait
- The inserted DNA
  - Transformation method
  - Plasmid
  - Molecular characterization
  - Stability
Elements of a Submission

- Basic Information
- Endogenous Substances
- Added Substances
- Labeling

> The composition
- Toxicants, anti-nutrients
- Key nutrients
- Characterize intentional changes
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**
  - New proteins
    - Toxicity and allergenicity assessment
    - Bioinformatics and stability/digestibility
  - New metabolic pathways
    - Safety assessment

- **Endogenous Substances**

- **Added Substances**

- **Labeling**
Evaluating new substances for safety

• **What is it?**
  – Prior knowledge
  – What happens after consumption? (ADME)
  – What do we know about potential toxicity?

• **How much is safe to consume?**
  – Are feeding studies needed?
  – NOAEL (no-observed-adverse-effect-level)

• **How will this use of the substance change exposure levels?**
  – Calculating exposure

• **Are expected exposure levels safe?**
  – Margin of exposure
  – Safety standard: “Reasonable certainty of no harm”
Elements of a Submission

- Basic Information
- Endogenous Substances
- Added Substances
- Labeling
  - Common or usual name
  - “Material” differences?
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# 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>190</td>
<td>Insect resistance</td>
<td>cotton</td>
<td>MON89792, MON-88702-4</td>
<td>Sep 21, 2018 (PDF, 66 kB)</td>
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<td>159</td>
<td>Insect resistance</td>
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<td>CTC175-A</td>
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<td>158</td>
<td>Change in composition (Production of provitamin A carotenoids)</td>
<td>Rice</td>
<td>GR2E IR-000GR2E-5</td>
<td>May 24, 2018 (PDF, 88 kB)</td>
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<td>Insect Resistance</td>
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<td>Huahui No.1 HZU-HH001-9</td>
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<td>157</td>
<td>Male Sterility and Herbicide Tolerance</td>
<td>Canola</td>
<td>MS11 BCS-BN012-7</td>
<td>Oct 20, 2017 (PDF, 39 kB)</td>
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<td>155</td>
<td>Altered growth properties</td>
<td>Soybean</td>
<td>HB4 IND-00410-5</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>
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<tr>
<td>153</td>
<td>Change in composition (other) and pest resistance</td>
<td>Potato</td>
<td>Y8 SPS-000Y9-7</td>
<td>Feb 21, 2017</td>
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<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>
<td>Insect resistance and herbicide tolerance</td>
<td>Corn</td>
<td>MZIR088 SYN-00086-3</td>
<td>Apr 29, 2016</td>
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<td>148</td>
<td>Herbicide tolerance</td>
<td>Corn</td>
<td>MON 87410, MON-87419-8</td>
<td>Mar 11, 2016</td>
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<td>150</td>
<td>Herbicide tolerance</td>
<td>Corn</td>
<td>MZHGQUG SYN-000UG-2</td>
<td>Feb 23, 2016</td>
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<td>146</td>
<td>Altered composition (other) and Blight Resistance</td>
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<td>147</td>
<td>Altered Growth Properties</td>
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<td>Insect Resistance</td>
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<td>MON 87751, MON-87751-7</td>
<td>May 27, 2015</td>
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<td>132</td>
<td>Change in Composition (other)</td>
<td>Apple</td>
<td>GD743 SPS-00272</td>
<td>Mar 20, 2015</td>
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</table>

100+ consultations completed

www.fda.gov/bioconinventory
Completed Consultations
Crops (# of events)

- Corn (45)
- Potato (38)
- Soybean (20)
- Canola (19)
- Cotton (25)
- Other* (14)

- Tomato (7)
- Radicchio (3)
- Alfalfa (3)
- Sugar beet (3)
- Rice (4)
- Other* (14)

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

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

* Plant-incorporated protectants regulated by EPA
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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>
<th>Date Received Submission - file size</th>
<th>Date of FDA’s Response Letter</th>
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</thead>
<tbody>
<tr>
<td>18</td>
<td>AC1 glucanase</td>
<td>Agrivida, Inc.</td>
<td>Oct 5, 2017 (3.7 MB)</td>
<td>Feb 21, 2018 (227 kB)</td>
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<td>17</td>
<td>isopentenyltransferase (IPT)</td>
<td>Arcadia Biosciences, Inc.</td>
<td>Apr 3, 2017 (PDF, 8.1 MB)</td>
<td>Jun 23, 2017 (PDF, 39 kB)</td>
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<td>16</td>
<td>homeobox domain HAHB4 protein (HAHB4)</td>
<td>Verdea, Inc.</td>
<td>Apr 22, 2015 (PDF, 568 kB)</td>
<td>Aug 7, 2015</td>
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<td>14</td>
<td>trypsin</td>
<td>Applied Biotechnology Institute</td>
<td>Mar 25, 2015 (PDF, 148 kB)</td>
<td>Sep 2, 2015</td>
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<tr>
<td>12</td>
<td>5-enolpyruvate shikimate-3-phosphate synthase (EPSPS ACE5)</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 28, 2010 (withdrawn*)</td>
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<td>9</td>
<td>aryloxyalkanoate dioxygenase-12 (AAD-12)</td>
<td>Dow AgroSciences LLC</td>
<td>Dec 17, 2008 (PDF, 1384 kB)</td>
<td>May 19, 2010</td>
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<td>Sep 13, 2007 (PDF, 552 kB)</td>
<td>May 19, 2010</td>
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<td>aryloxyalkanoate dioxygenase 1 (AAD 1)</td>
<td>Dow Agrosciences LLC</td>
<td>Mar 28, 2007 (PDF, 27 kB)</td>
<td>Dec 22, 2009 (withdrawn*)</td>
</tr>
</tbody>
</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
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

• Points of contact
  – Biotechnology Consultation Program: [robert.merker@fda.hhs.gov](mailto:robert.merker@fda.hhs.gov)
  – New Protein Consultations: [carrie.mcmahon@fda.hhs.gov](mailto:carrie.mcmahon@fda.hhs.gov)