



FDA Regulation of Products Derived from Genetic Engineering

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Ritu Nalubola, Ph.D.
Senior Policy Advisor
Office of Policy, Office of the Commissioner



Briefly today . . .

- FDA's mission
- Biotechnology in FDA-regulated products
- U.S. Coordinated Framework
- Regulation of human & animal food derived from GE plants
 - 1992 policy statement
 - Premarket consultation process
- Regulation of GE animals
 - Guidance for industry (GFI) 187
 - New animal drug approval process

What does FDA do?

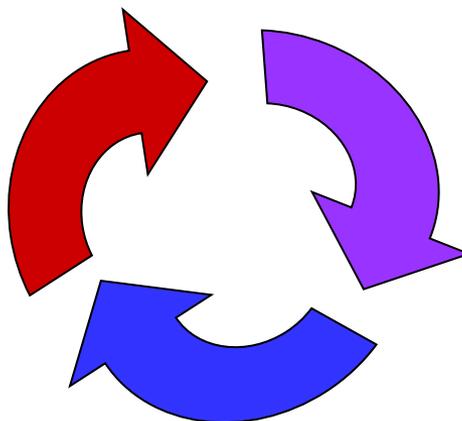
FDA is responsible for:

- Protecting the public health by assuring that foods are safe, sanitary, and properly labeled; ensuring that human and veterinary drugs, and human vaccines and other biological products and medical devices are safe and effective
- Protecting the public from electronic product radiation
- Assuring cosmetics are safe and properly labeled
- Regulating tobacco products
- Advancing the public health by helping to speed product innovations

FDA's Core Business Functions

Pre-Market Review

Assessment of safety and effectiveness of new medical technology & safety of new food ingredients



Product Safety & Compliance

Inspection of facilities and products to assure safety, quality & compliance with FDA regulations

Consumer & Patient Safety

Post-marketing surveillance to ensure the safety of consumers & patients who use FDA-regulated products

Biotechnology and FDA Products

- Drugs, including biological products
 - Human drugs
 - Animal drugs
- Food/food additives
 - Food for humans
 - Food for animals

Focus of this presentation is on regulation of: (1) human and animal food derived from GE plants; and (2) GE animals

Coordinated Framework

- FDA regulation is based on the rational and scientific evaluation of products, and not on *a priori* assumptions about certain processes.
- Congress has provided FDA authority to regulate products regardless of how they are manufactured.
- Review of products using biotechnology is based on the intended use of each product on a case-by-case basis.
- FDA will evaluate products in cooperation with USDA and EPA, where appropriate.

51 FR 23309, June 26, 1986

Regulation of food derived from GE plants



Relevant Statutory Provisions for Foods from GE Plants

Federal Food, Drug, and Cosmetic Act (FD&C Act)

- To ensure safety, FDA relies primarily on:
 - Section 402 - Adulterated Food
 - Section 409 - Food Additives

Adulterated Food Provision

- A food is deemed adulterated and thus unlawful if it bears or contains an added poisonous or deleterious substance that may render the food injurious to health or a naturally occurring substance that is ordinarily injurious.

For example, this provision would apply to a naturally occurring toxin in food if the level of the toxin in a new plant variety were increased through traditional plant breeding, genetic engineering, or some other human intervention.

Food Additive Provisions (1)

- A food additive is broadly defined to include any substance the intended use of which results or may be reasonably expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of food, unless the substance is generally recognized as safe (GRAS) under conditions of its intended use, subject to certain exceptions.
- With respect to food additives and GRAS substances, safe or safety means *there is a reasonable certainty that the substance is not harmful under the intended conditions of use* (21 CFR 170.3(i))

Food Additive Provisions (2)

- Food additives must be approved by FDA prior to market.

It is the transferred genetic material and the intended expression product(s) that could be subject to food additive regulation, if such material or expression products are not GRAS for the intended use.

1992 Policy Statement

“Statement of Policy: Foods Derived from New Plant Varieties” (57 FR 22984, May 29, 1992)

- Foods derived from plant varieties developed by the new methods of genetic modification (e.g., genetic engineering) are regulated within the existing framework of the FD&C 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.

Premarket Consultation Process (1)

1997 Guidance for Industry – Consultation Procedures for Foods Derived from New Plant Varieties (originally issued in 1996; updated in 1997)

- Participation in process is voluntary, but compliance with law is not.
- Consultation process:
 - Provides for rigorous case-by-case food safety evaluation that is consistent with international guidelines.
 - Allows firms a premarket opportunity to ensure their foods meet applicable safety and other regulatory requirements, including identifying safety and/or regulatory issues.

Premarket Consultation Process (2)

What does FDA do during its evaluation of a consultation submission?

- FDA evaluates data and information to identify any unresolved food safety, nutritional, or other issues.
- FDA does not complete a consultation until it is satisfied that all safety and other regulatory issues have been resolved.
- Once the consultation is complete, FDA sends a “no questions letter” to the firm and completed consultations are disclosed on FDA’s website at www.fda.gov/bioconinventory.

Data & Information Typically Considered During Premarket Consultation

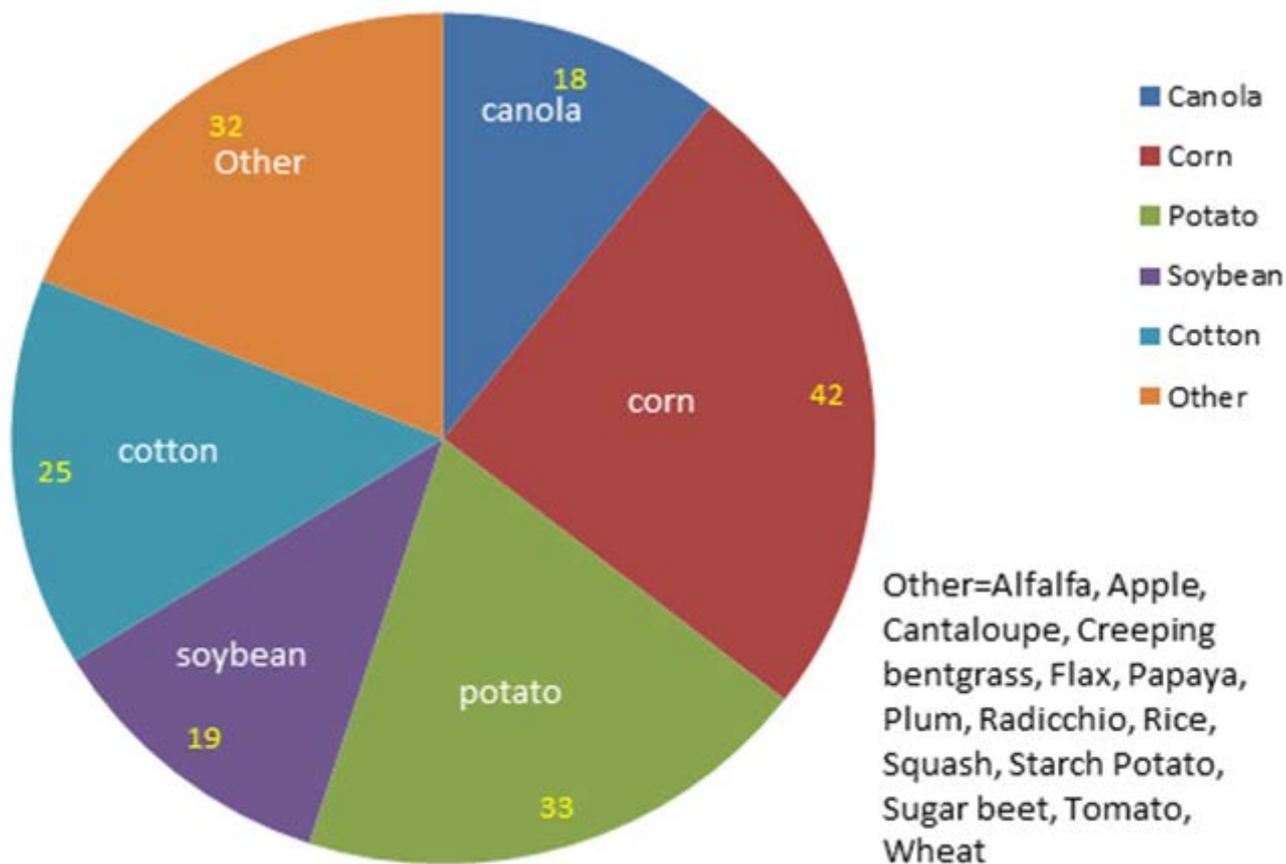
- What is the crop?
 - What are the human and animal food uses of the crop?
 - What is the purpose or intended technical effect of the modification in the crop?
- Safety assessment components
 - Molecular characterization to aid in identifying what is new/changed in the food that may impact safety/nutrition
 - Safety of newly expressed substances
 - Potential toxicity of newly expressed substances
 - Potential allergenicity of newly expressed proteins
 - Levels of key nutrients, anti-nutrients, and toxicants in food from the plant
- Assessment is performed on a case-by-case basis

Biotechnology Consultations on Food from GE Plant Varieties (1)

To date, FDA has completed over 100 consultations and evaluated over 150 plant varieties.

- FDA has evaluated genetically engineered varieties of soybean, corn, cotton, canola, papaya, alfalfa, creeping bent grass, plum, potato, sugar beet, wheat, rice, cantaloupe, flax, squash, and radicchio.
- Plant varieties have expressed traits such as herbicide tolerance, insect resistance, virus resistance, altered ripening, nutritional composition changes, altered plant fertility, and altered plant growth properties.

Number of Events in Completed Consultations by Crop



Biotechnology Consultations on Food from GE Plant Varieties (2)

- Thus far, most added substances considered during consultations have been presumed GRAS due to their similarity to substances already safely consumed in the food supply.
- However, there have been other substances. For example:
 - An enzyme (derived from a GE plant variety) that provides resistance to the antibiotic kanamycin, was evaluated as a food additive and approved for use in tomato, canola, and cotton (21 CFR 173.170; 573.130)

Use of GE Microorganisms in Food

- Foods (for humans or animals) produced using GE microorganisms are regulated like any other substance added to food.
 - Approval of a food additive petition is required prior to marketing unless use of the substance is GRAS.
 - If use of the substance is GRAS, firms may voluntarily choose to notify FDA of their GRAS determination by submitting a GRAS notice to FDA.

Regulation of Genetically Engineered Animals



Relevant Statutes for Products of GE Animals

Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Section 201 -- Definition of drug; Definition of new animal drug (NAD);
- Section 512 – New animal drug provisions; Investigational new animal drug (INAD) exemption

National Environmental Policy Act (NEPA)

- Directs agencies to evaluate environmental impacts of “agency actions”

New Animal Drug Provisions

- Prohibits introduction of unapproved drug into commerce
 - Drugs are *articles* intended to
 - Diagnose, cure, mitigate, treat, or prevent disease
 - Intended to affect the structure or any function of the body
- Exemption for research
 - Investigational use
- For approval, sponsor of application must demonstrate
 - Safety to animal
 - Food safety (if a food animal)
 - Effectiveness (does the article do what the sponsor claims?)

Guidance for Industry (GFI) 187

Guidance 187: Regulation of Genetically Engineered Animals Containing Heritable recombinant DNA constructs

- Clarification of FDA's continued regulation of GE animals under NAD provisions of FD&C, and NEPA
- Congruence with existing regulations
 - 21 CFR 511 (INAD)
 - 21 CFR 514 (NADA)
 - 21 CFR 25 (NEPA)
- Recommendations on how sponsors can prepare data and information for FDA to review

Key Concepts

- Covers all GE animals bearing heritable rDNA constructs (including biopharm animals)
- *The rDNA construct in a GE animal that is intended to affect the structure or function of the body of the GE animal, regardless of the intended use of products that may be produced by the GE animal, meets the FD&C drug definition*
- Case-by-case evaluation; Risk-based approach
- Mandatory approval prior to marketing of NADs (i.e., new animal drug application (NADA))

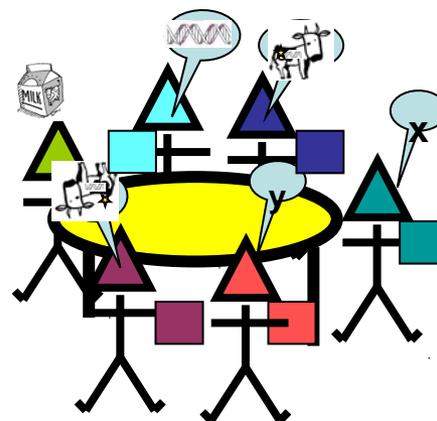
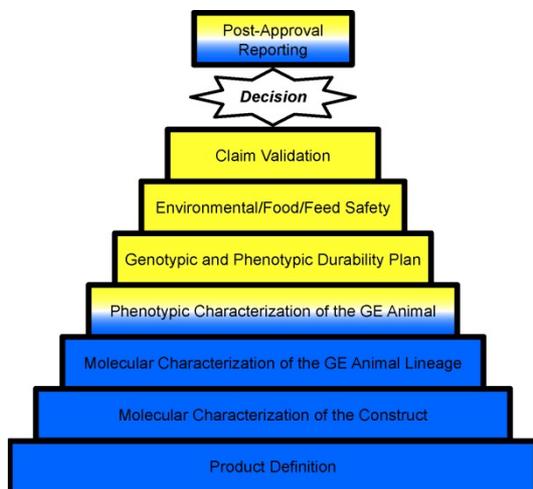
Data & Information in INAD & NADA Submissions

- **Investigational New Animal Drug (INAD)**
 - INAD file should include information about the GE animal, e.g., species of animal under study, introduced gene(s), intention of modification, including any gene product(s) produced
 - In general, INAD regulations specify:
 - Labeling and record-keeping requirements
 - Animal disposition
 - NCIE Notice, prior to shipping any GE animals
 - Environmental considerations
- **Recommended process for submitting data for GE animal New Animal Drug Application (NADA)**
 - Product identification
 - Molecular characterization of the construct
 - Molecular characterization of the GE animal lineage
 - Phenotypic characterization of GE animal
 - Genotypic and phenotypic durability assessment and durability plan
 - Food/feed safety and environmental safety assessments
 - Effectiveness/claim validation

The NADA/INAD Review Process

Hierarchical, weight-of-evidence, risk-based

- Satisfies statutory requirements for safety, effectiveness
- Follows NADA regulations
- Team-based review



FDA's First Approval of an rDNA Construct in a GE Animal: GTC's ATryn[®] Producing GE Goats



2 Separate Regulatory Actions

- CVM NADA approval
 - rDNA construct in GE goat to produce rh antithrombin in milk
- CBER biologics license application approval for ATryn
 - Anticlotting agent for individuals with a hereditary clotting disorder in high-risk situations



For additional information

GE Plants:

<http://www.fda.gov/Food/FoodScienceResearch/Biotechnology/default.htm>

GE Animals:

<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/default.htm>

