wiley

Food Derived from Biotechnology: The Future of Food

March 29, 2022

Ann M. Begley
Partner
202.719.4585
ABegley@wileyrein.com

Agenda

- Coordinated Framework for Regulation of Biotechnology
- Regulation of Food Derived from Genetically Engineered Plants/Crops
- Regulation of Foods Derived from Genetically Engineered Microorganisms
- Regulation of Foods Derived from Genetically Engineered Animals
- The Regulation of Foods Derived from Animal Cell Lines

The Coordinated Framework

First published in 1986 by the White House Office of Science and Technology Policy (OSTP)

- Described a comprehensive federal regulatory policy to assure the safety of biotechnology products
  - To protect health and environment without impeding innovation

Updated in 1992 to adopt a risk-based, scientifically sound framework

- Affirmed that federal oversight should focus on product characteristics and the environment in which it is introduced rather than the process by which it is created

Update in 2017 to clarify roles and responsibilities among the primary agencies

- Describes communications among the Agencies

Three Primary Agencies aim to cover the full range of plants, animals and microorganisms derived from biotechnology in an integrated and coordinated manner

- EPA
- USDA
- FDA

The Coordinated Framework – Environmental Protection Agency (EPA)

Regulation of Pesticides

- Authorizing Statutes: Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
- Federal Food, Drug and Cosmetic Act (FFDCA) section 408, EPA establishes the amount of pesticide chemical residues that may be present in food.
  - Plant-incorporated protectants (PIPs)

Regulation of Microorganisms

- Authorizing Statute: Toxic Substances Control Act (TSCA)
  - Foods, drugs, cosmetics, and medical devices subject to the FFDCA excluded

The Coordinated Framework – USDA

Animal and Plant Health Inspection Service (APHIS): responsible for protecting agriculture from pests and diseases

- Authorizing Statutes:
  - Animal Health Protection Act (AHPA) and Plant Protection Act (PPA): Regulate biotechnology derived products that may pose a risk to agricultural plant and animal health.
  - Virus-Serum-Toxin Act (VSTA), USDA regulates products of biotechnology included in veterinary biologics for purity, safety, potency, and effectiveness.

Food Safety and Inspection Service (FSIS): responsible for ensuring the commercial supply of meat, poultry, certain egg and fish products is safe, wholesome, and correctly labeled, including those products derived using genetic engineering

- Authorizing Statutes
  - Federal Meat Inspection Act (FMIA)
  - Poultry Products Inspection Act (PPIA)
  - Egg Products Inspection Act (EPIA)

The Coordinated Framework – FDA

FDA is responsible for the safety of drugs, biologics, medical devices, and most foods for humans and animals, including those produced using biotechnology

Authorizing Statutes:

- The Federal Food, Drug, and Cosmetic Act
- The Public Health Services Act.

Regulation of Food Derived from Genetically Engineered Plants/Crops

Genetically Engineered Plants Controlling Pests – What Agency regulates this?

- Corn plant genetically engineered to express protein derived from B. thuringiensis to resist moth insects.

USDA Regulation of Genetically Engineered Plants – (7 C.F.R. Part 340 – APHIS Permit Process)

- New **GE Plant**: unless otherwise exempt, must be reviewed by APHIS to determine whether it presents no more of a **plant pest risk** than the non-GE plant version or other appropriate comparator plant.
  - If the GE plant is determined not to present a plant pest risk, it is not subject to special regulation by APHIS
  - If the GE plant is determined to present a plant pest risk, the owner must apply for a **Permit** that tightly controls the movement of the plant.
- **Plant pest**: any living [article] that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product.
- **Plant pest risk**: The potential for injury to, damage to, or disease in any plant or plant product resulting from introducing or disseminating a plant pest, or the potential for exacerbating the impact of a plant pest.

USDA Regulation of Genetically Engineered Plants – APHIS (cont.)

Regulatory Status Review (Initial or Re-Review) of GE Plant:

- Submission for Review or Re-Review Request
  - Description of the comparator plants, including genus, species, and relevant subspecies information
  - Genotype of the GE plant, including a description of the differences in genotype between the GE plant and the non-GE plant, and
  - Detailed description of the new traits of the modified plant

- Generally, a 180 day initial or re-review period except under circumstances that could not be reasonably anticipated
  - If determined not to be a plant pest risk, APHIS will publish the determination on its website.
  - If determined to be a plant pest risk, requestor can apply for a permit, or request an Evaluation of the factors of concern
    - If requestor seeks an Evaluation, the results of the APHIS evaluation will be published in the Federal Register for public comment. This step is generally completed within 15 months of receipt of review request.
    - Possible Outcome of Evaluation
      - Not a pest – Published in Federal Register and on APHIS website
      - A Pest – Permit Required

The Regulation of Genetically Engineered Plants – APHIS Permits for GE Organisms

Submission of a permit application

- For interstate movement/import
- For release into the environment

Permit conditions

- Maintained/disposed in a manner that prevents unauthorized release, spread, dispersal and/or persistence in the environment
  - Permit will specify such measures
- Maintained separate from other organisms except as specifically allowed
- Maintained in areas/premises allowed by the permit
- The identity of the BE plant must be maintained and verifiable at all times
- Permit is only valid for a specified period of time.
- Record maintenance
- Agreement to inspections
- Notify APHIS within 24 hours of discovery or of possible or actual release contrary to the Permit restrictions
- Identify a Responsible Person

Regulation of Food Derived from Genetically Engineered Crops – FDA

- **FDA Voluntary Consultation Programs**

  - **Plant Biotechnology Consultation Program**
    - Commenced in 1992 to support developers in confirming that their new foods are “safe and lawful” prior to marketing.
    - Over 160 consultations
    - No significant timelines imposed on FDA – can go on for years (typically 1.5-3 years from time of final submission)

  - **New Protein Consultation Program (Early Food Safety Evaluation)**
    - Commenced in 2006 to address gap in Plant Biotechnology Consultation Program
    - Only Addresses evaluation of inadvertent, low-level presence of new protein in food to determine if the protein is an allergen or a toxin
    - FDA Guidance provides for more strict timelines than Plant Biotech Program – Should be complete within 1 year of submission.

While these programs are identified as *voluntary*, going to market without participating in these programs could result in FDA enforcement action

FDA's Plant Biotechnology Consultation Program

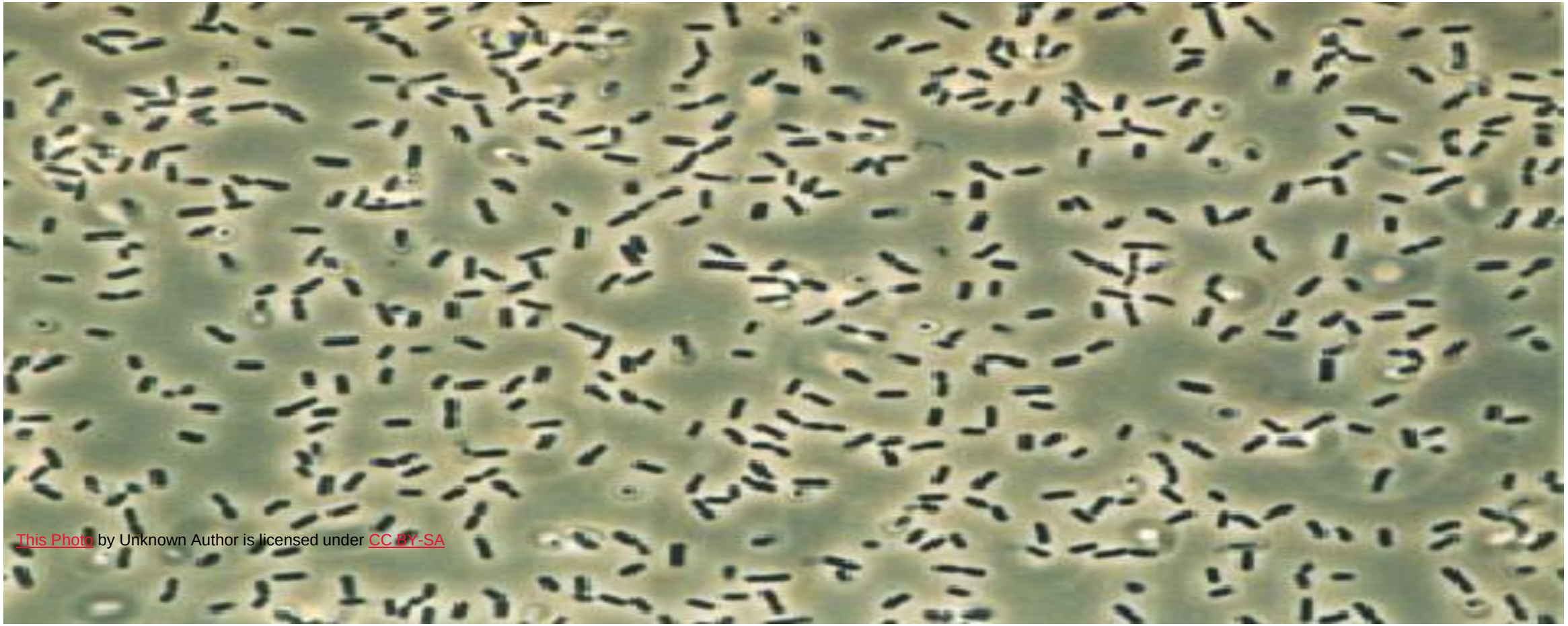
Initial Consult	• Multiple meetings and communications between Developer and FDA Biotechnology Team
Final Consult	• Developer submits notification of intent to market • Additional meeting(s) with Developer
FDA Final Letter: possible outcomes	• No Questions • The food is subject to a food additive petition • Other regulatory issues (e.g., labeling)

FDA's Plant Biotechnology Consultation Program – Some Resource Links/Updates

- Some Resource Links:
  - FDA's Biotechnology Guidance Documents & Regulatory Information Page
  - FDA's completed New Plant Variety Consultations
  - FDA's completed new protein consultations

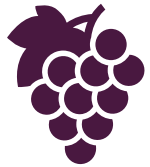
- Update: FDA Draft Guidance under development:
  - Foods Derived from Plants Produced Using Genome Editing (Constituent Update, January 31, 2022)

Regulation of Foods Derived from Genetically Engineered Microorganisms



Regulation of Foods Derived from Genetically Engineered Microorganisms

Products of Fermentation frequently employ a microorganism, many of which are genetically engineered to enhance existing function or impart new functionality to that organism



Examples of foods produced by fermentation

***Enzymes**

***Sweeteners**

***Vitamins such as B12**

***Alternative protein sources**

Pathway to Market:

***Food Additive Regulation**

***GRAS Conclusion,**

***New Dietary Ingredient Notification**

Labeling:

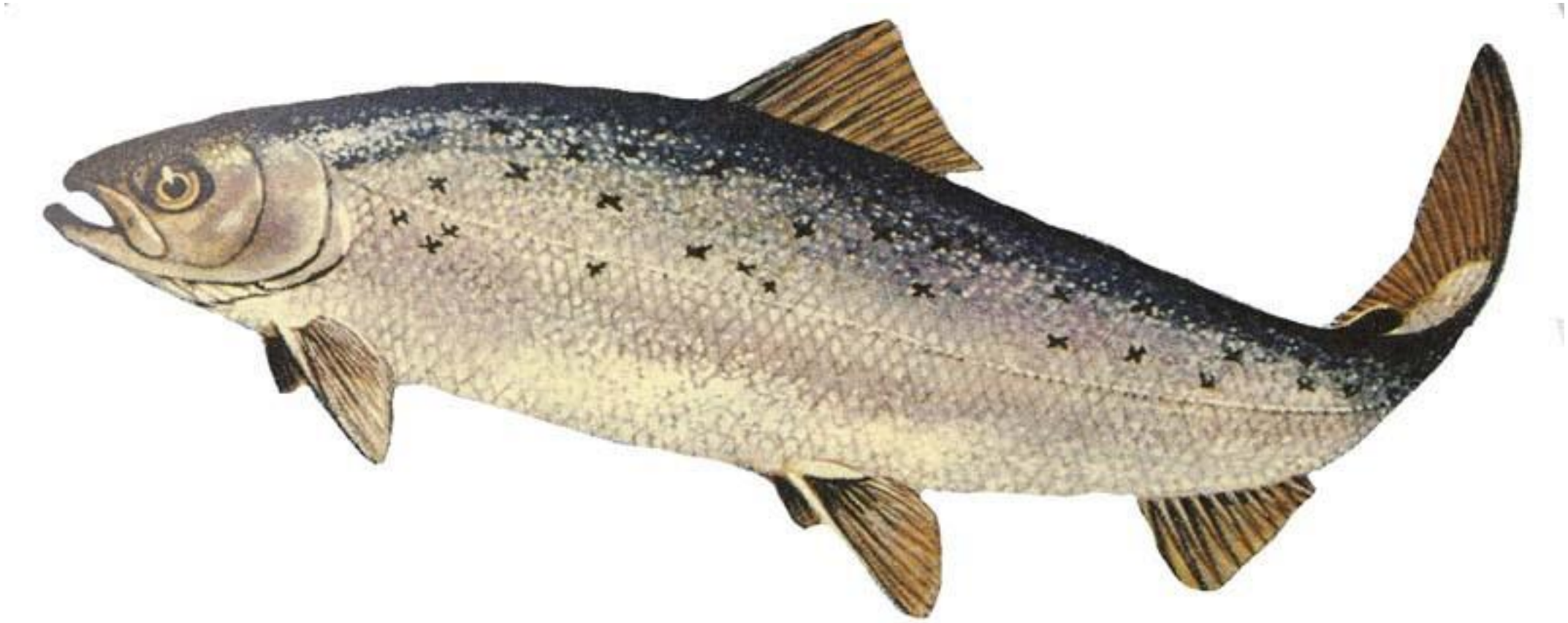
***FDA Draft Guidance under development*:**

***Labeling of plant-based Milk Alternatives**

***Labeling of plant-based alternatives to animal-derived foods**

(Constituent Update, January 31, 2022)

Regulation of Foods Derived from Genetically Engineered Animals



Regulation of Foods Derived from Genetically Engineered Animals – FDA

- FDA regulates the **intentional genomic alterations (IGA)** in animals as animal drugs because they alter the structure or function of the animal.

- The definition of a "drug" under Section 201(g) of the FFDCA includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) *intended to affect the structure or any function of the body of man or other animals*."

- The Center for Veterinary Medicine (CVM) leads this effort

Regulation of Foods Derived from Genetically Engineered Animals – FDA

CVM Review of a New Animal Drug Application (NADA) assesses the safety and effectiveness of the IGA

- Safe for the animal
- Safe for anyone that may consume food from the animal
- Effective i.e., it does what the developer claims it will do.

In addition, CVM conducts an Environmental Assessment* to determine whether the article poses a human, animal, or environmental risk, asking the following questions:

- does the altered genomic DNA contain sequences that can cause human or animal disease either intrinsically or by recombination?
- For environmental releases, does the animal with intentionally altered genomic DNA pose any more of an environmental risk than its counterpart?
- Are there concerns over the disposition of animals with intentionally altered genomic DNA that could pose human, animal, or environmental risks?

*See *Inst. for Fisheries Res. v. U.S. Food & Drug Admin.*, Case No. 16-cv-01574-VC (N.D. Cal. Nov. 5, 2020)

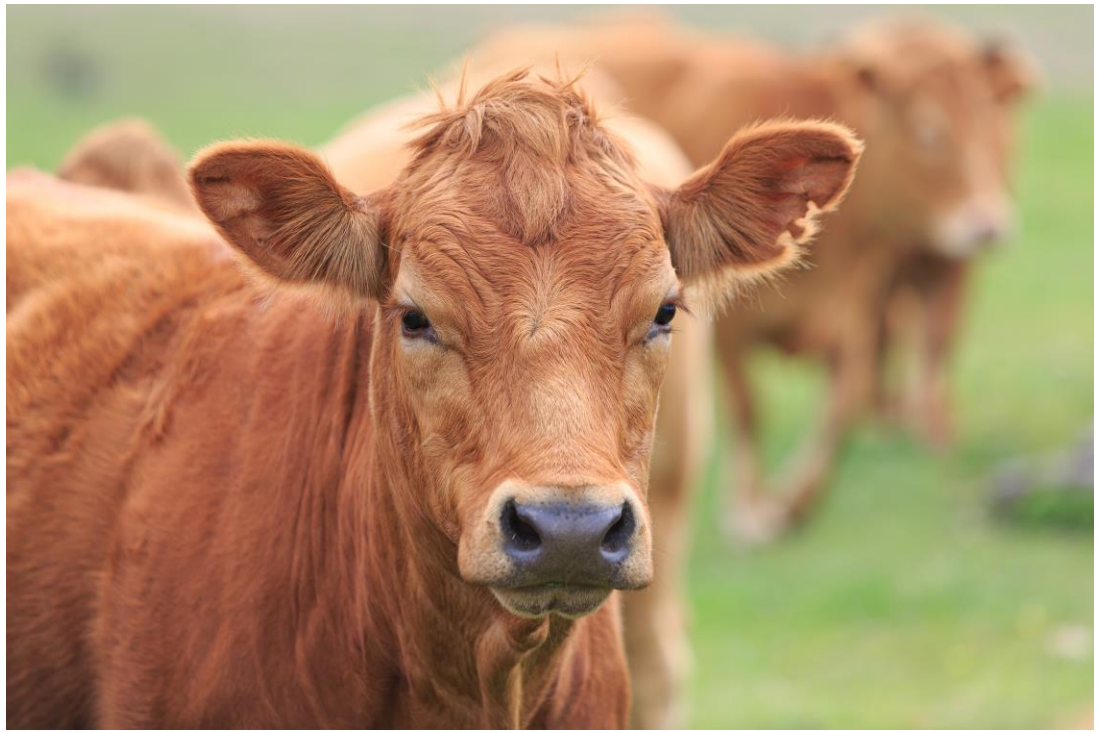
Low-Risk IGA Determination for Food Producing Animals: PRLR-Slick Cattle – genome edited – March 2022

FDA Enforcement Discretion

- FDA does not expect submission of a NADA
  - Case-by-case basis
  - FDA determination that the product or category is low risk to humans, animals and the environment

Factors for Low-Risk Determination for IGA contained in PRLR-Slick Cattle

- IGA is the equivalent genotype to naturally occurring mutations in several breeds raised in tropical or subtropical environments (with normal biological variability)
- IGA results in same phenotype (slick-hair trait) found in conventional cattle
- Reasonable certainty of no human food safety concern. Food products from IGA produced cattle are as safe as food products derived from conventionally bred cattle with same slick hair trait and commonly consumed by humans
- Animal safety profile same as in conventionally bred cattle with same genotype/phenotype
- IGA does not pose a risk to the environment with typical farm containment and practices
- Limited to “marketed products derived from the existing two cattle containing the IGA for which FDA has reviewed data and their progeny”



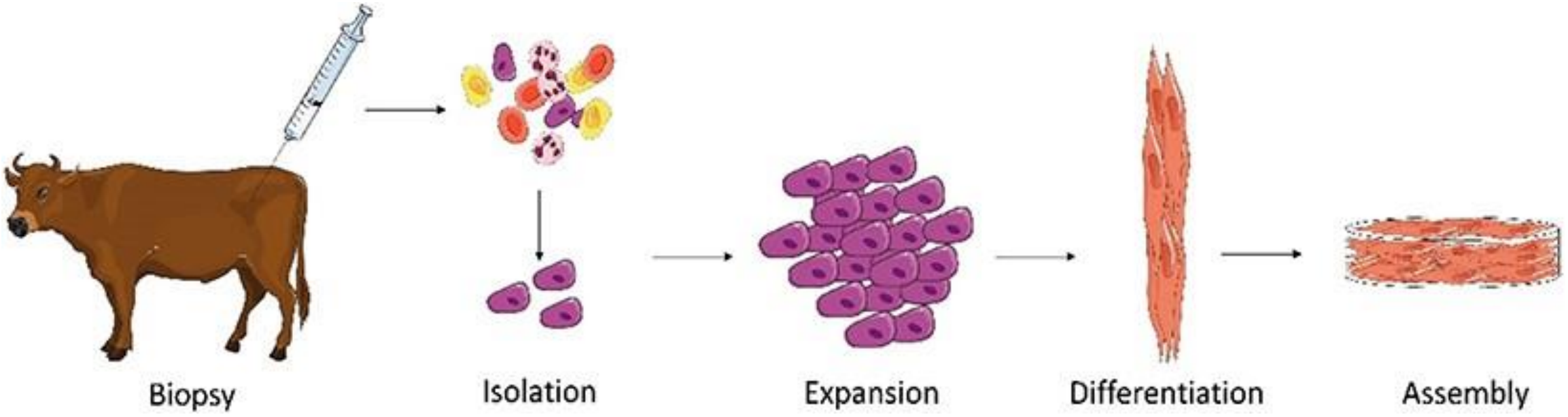
The Regulation of Foods Derived from Genetically Engineered Animals – January 2021 proposal

HHS/USDA Memorandum of Understanding to develop new framework for regulating genetically engineered animals (January 13, 2021) (comment period closed on May 7, 2021)

MOU Provisions:

- USDA will evaluate and regulate "agriculture amenable species developed using genetic engineering" under its existing authorities set forth in the Animal Health Protection Act, FMIA, and the PPIA.
  - FDA will be available to consult where concerns arise related to human health, and animal health or food safety matters that impacts human health if the concerns are not covered by the USDA process
  - Rulemaking required and must contain specific elements
- FDA will immediately implement a streamlined, risk-based approach to IGAs in animals
- FDA will retain authority over dairy products, table and shell eggs, certain meat products, and animal food, and over IGAs for non-agriculture use (e.g., gene therapies)

Regulation of Foods Derived from Animal Cell Lines



Formal Agreement Between HHS-FDA and USDA-FSIS – March 2019

Scope:

- Applies to animal cell culture technology using cells from livestock and poultry (Seafood, other than Siluriformes, remain solely under FDA jurisdiction)
- Only represents a “broad outline” of the Agencies’ present intentions.
- Provides that the Agencies will develop a more detailed joint framework, including joint principles for product labeling and claims to ensure consistency and transparency.

Substance:

- Broadly, the FDA will oversee cell collection, growth, and differentiation of cells through time of harvest. At harvest stage, oversight will transition to USDA to oversee production and labeling of cell-cultured meat (CCM)

Formal Agreement Between HHS-FDA and USDA-FSIS – March 2019

HHS-FDA primarily intends to:

- Conduct premarket consultation processes to evaluate production materials, processes, and manufacturing controls
- Oversee initial cell collection, cell lines and banks, and all components and inputs used in CCM production
- Oversee proliferation and differentiation of cells through time of harvest
- Ensure compliance with requirements regarding substances that become a component of food or otherwise affect the characteristics of food.

USDA-FSIS will obtain regulatory oversight from HHS-FDA at harvest, and primarily intends to:

- Require each CCM-harvesting establishment to obtain a USDA mark of inspection
- Conduct inspections in establishments where CCM is harvested, processed, packaged, or labeled, in accordance with FSIS regulations
- Require that the labeling of CCM products be pre-approved and then verified through inspection, as required by FSIS regulations
- Develop additional requirements as needed to ensure accurate labeling of CCM products

Formal Agreement Between HHS-FDA and USDA-FSIS – Updates

September 3, 2021, USDA-FSIS published ANPRM to request comments on labeling of meat and poultry products derived from animals subject to FMIA and PPIA. (86 Fed.Reg. 494941)

October 7, 2020, FDA issued a similar document (request for information) seeking comments on cell-cultured seafood subject to FDA's regulation.

January 31, 2022: FDA announced plans to develop a draft guidance: premarket consultations on cultured animal cell foods

Cell-Cultured Meat Approved Elsewhere!

Singapore issued first regulatory approval for lab-grown meat to Eat Just in December 2020

Key Take Aways

- The regulation of GE foods spans several agencies and several programs within those agencies. Take care to see where your product fits!
- The US oversight framework for GE foods continues to evolve with an ongoing focus on assuring safety without hindering innovation
- The impact of GE foods on the environment will remain an important part of the GE food evaluation process
  - Impact on non-GE plants and animals
  - Impact on reducing green house emissions, land use, etc.

For questions contact:

Ann Begley
Wiley Rein LLP
202.719.4585
abegley@wiley.law