Food Products Incorporating Cultured Animal Cells
Regulatory Perspectives

Wednesday, September 25, 2019

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Overview of Agenda

Animal Cell Culture Overview

Overview of Joint Framework

FDA Experience

Next Steps
Animal cell culture food technology refers to the controlled growth of animal cells from livestock, poultry, fish, or other animals, their subsequent differentiation into various cell types, and their collection and processing into food.
Development of Animal Cell Culture Technology

• Research tool
  – Growing animal cells to study basic biology
  – Moving from specialized cells to tissues

• Therapeutic application
  – Production of protein biologics
  – Clinical use of single cells, tissues, and organs

• Food production
  – Tools/methods from therapeutics currently available
  – Challenges remain in scaling production technologies
Overview of Animal Cell Culture Technology

Cell Procurement and Qualification
- Tissue Collection
- Liberation of Cells from Tissue
- Cell Collection
- Master Cell Bank Creation
- Master Cell Bank Qualification

Cell Proliferation
- Growth Factors
  - Cytokines
  - Hormones
  - Signaling Molecules
  - Gases (O₂, CO₂)
- Nutrients
  - Vitamins
  - Sugars
  - Fats
  - Minerals
  - Amino Acids

Cell Differentiation and Preparation
- Growth and Differentiation Factors
  - Cytokines
  - Hormones
  - Signaling Molecules
- Mechanical Differentiation Signals
- Scaffold and Structure Components
- Plant-Derived Components
- 3D Cell Printing
- Recombinant Microbes
- Gases (O₂, CO₂)
- Nutrients

Post-Harvest Processing
- Conventional Food Processing Technologies
- Harvested Nonviable Cellular Material
- Post-Harvest Processing

Finished Food
Joint Framework – Roles and Responsibilities

FDA
- Cell banks
- Cell culture

FSIS
- Processing
- Packaging, labeling

Detailed process
Regulatory analysis
Joint labeling policy

Overview of Joint Framework
Joint Framework – FDA Roles and Responsibilities

• Conduct premarket assessments for cell culture processes
• Oversee
  – Cell collection
  – Cell bank maintenance
  – Cell proliferation and differentiation
• Conduct inspections and enforcement activities to ensure cell bank and culture facilities are in compliance with FFDCA requirements
• Oversee
  – post-harvest safety of products incorporating cultured fish and seafood cells (except Siluriformes)
  – labeling of products incorporating cultured fish and fishery product cells (except Siluriformes)
Joint Framework – USDA Roles and Responsibilities

• To require establishments that harvest and/or process cultured livestock and poultry cells to obtain a grant of inspection

• To conduct inspection in such establishments to ensure that products are safe, wholesome, and properly labeled, as well as

• To require preapproval and verification for labeling of these products
Joint Framework – Shared Roles and Responsibilities

• Develop more detailed joint framework for oversight transfer at harvest for cells from amenable species
• Develop coordinated labeling policy to ensure consistent labeling of all foods incorporating cultured animal cells
• Jointly assess future regulatory/statutory needs
• Collaborate on investigation of any food safety issues
FDA’s Regulatory Framework and Relevant Experiences

- Regulatory approach for food/food ingredients
- Relevant experiences in foods
- Relevant experiences in therapeutics
Systems-Based Oversight and Mandatory Food Safety Plans

• Hazard analysis
  – Known or reasonably foreseeable
  – Biological, chemical, physical hazards

• Preventive controls
  – Process, allergen, sanitation, other as needed

• Oversight and management of controls
  – Monitoring, correction, corrective action, verification

• Supply chain program
  – If needed based on hazard analysis

• Recall plan
Food Additives

Any substance the intended use of which results or may reasonably be expected to result in its becoming a component or otherwise affecting the characteristic of any food, including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting or holding food.

FDA Experience
Reasonable Certainty of No Harm

Identity and Exposure

Relevant Properties

Appropriate Data

FDA Experience
Examples from Past Experience

- Substances produced by cultured cells
- Cultured cells for direct consumption
- New plant varieties produced by modern biotechnology
Substances Produced by Cultured Cells

- Enzymes
- Oils
- Transgenic proteins

FDA Experience
Cultured Cells Evaluated as Direct Food Ingredients

FDA Experience
New Plant Varieties Produced Using Modern Biotechnology

Unexpected or unintended effects

Safety assessment: the host plant (Figure 2)

If food from the donor is commonly allergenic, can it be demonstrated that the allergenic determinant has not been transferred to the new variety?

Yes

No

Yes

No

Consult FDA

Have safety concerns about host-associated toxicants and donor-associated toxicants been addressed?

Yes

No

Are the concentration and bioavailability of important host-associated nutrients within range?

Yes

No

Consult FDA

New variety not acceptable

Yes

No

Are the introduced proteins likely to be a macroconstituent in the human or animal diet?

Yes

No

Consult FDA

No concerns

Yes

No

Are there any unusual or toxic components?

Are there any alterations that could affect nutritional qualities or digestibility in a macroconstituent of the diet?

Yes

No

Consult FDA

No concerns

Yes

No

Expected or intended effects

Safety assessment: the donor(s) (Figure 3)

Safety assessment: introduced proteins in new variety (Figure 4)

Safety assessment: new or modified carbohydrates, fats or oils in new variety (Figures 5 and 6)

Are there any reported toxicity, or does the biological function raise any safety concern?

Yes

No

Consult FDA

Is there any FDA Experience

Figure 1. Safety Assessment of New Varieties: Summary
Current Uses of Cell Culture in Clinical Application

- Cells as a source of production for
  - Recombinant proteins
  - Viruses
  - Vaccines
- Cells as therapies
- Cells that are genetically modified (ex vivo modified cells)
- Cells that are grown in materials/scaffolding
Risk-Based Control in Clinical Applications

**Challenges**
- Source contamination
- In-process contamination
- Purity of the product
- Use of matrix/scaffold
- Scale up

**Controls**
- Identification of potential risks
- Process control
- Quality assurance
- Inspection
- Record implementation

FDA Experience
Observations from Past Experience

• Biological production systems can be complex
• Questions about consistency and control of outcomes often arise during the safety evaluation
• These questions can be successfully addressed during the safety evaluation process prior to market entry
• Risk-based preventive controls can be used to ensure that the process generates safe products
FDA Premarket Assessment

• FDA will develop a premarket assessment process for cellular material production processes to ensure that no issues arise under FFDCA Section 402 or 409
• Includes evaluation of inputs including cells, medium components, scaffolding, as well as properties of pre-harvest cellular material
• Identification of unresolved 409 or 402 issues could render food unlawful
• Also expect to assess facility food safety plans
FDA Verification and Enforcement

- Establishments that conduct cell banking, cell proliferation and differentiation, and cell harvest activities will be required to comply with current GMP and preventive control requirements for food production facilities.

- Once a facility is in production, FDA will conduct routine inspections of establishments that conduct preharvest and harvest activities:
  - The food safety plan evaluation will guide inspections.
  - Ongoing documentation of controls will be required.
  - Batch records will be important.
  - Records will include information relevant to safety, which we expect to include material inputs, cell sources and qualification, adventitious agent testing, and characterization of cellular material at harvest.

Next Steps
Joint Framework – USDA Roles and Responsibilities

• Require establishments that harvest and/or process cultured livestock and poultry cells to obtain a grant of inspection

• Conduct inspection in such establishments to ensure that products are safe, wholesome, and properly labeled, and

• Require preapproval and verification for labeling of such products
FDA’s Next Steps

• Develop, in consultation with FSIS
  – a general and systematic assessment for this food production technology to the point of harvest that will support individual premarket assessments.
  – draft guidance on preparing for and participating in premarket assessments for cellular material production processes, and on how manufacturers can ensure that their processes and products are in compliance with the applicable requirements of the FFDCA

• We will seek public comment and other forms of stakeholder input on these documents

• FDA and FSIS also expect to develop more detailed procedures to facilitate coordination of our shared regulatory oversight for cultured cells from amenable species