U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

# Approach to the safety assessment of protein ingredients for use in human food

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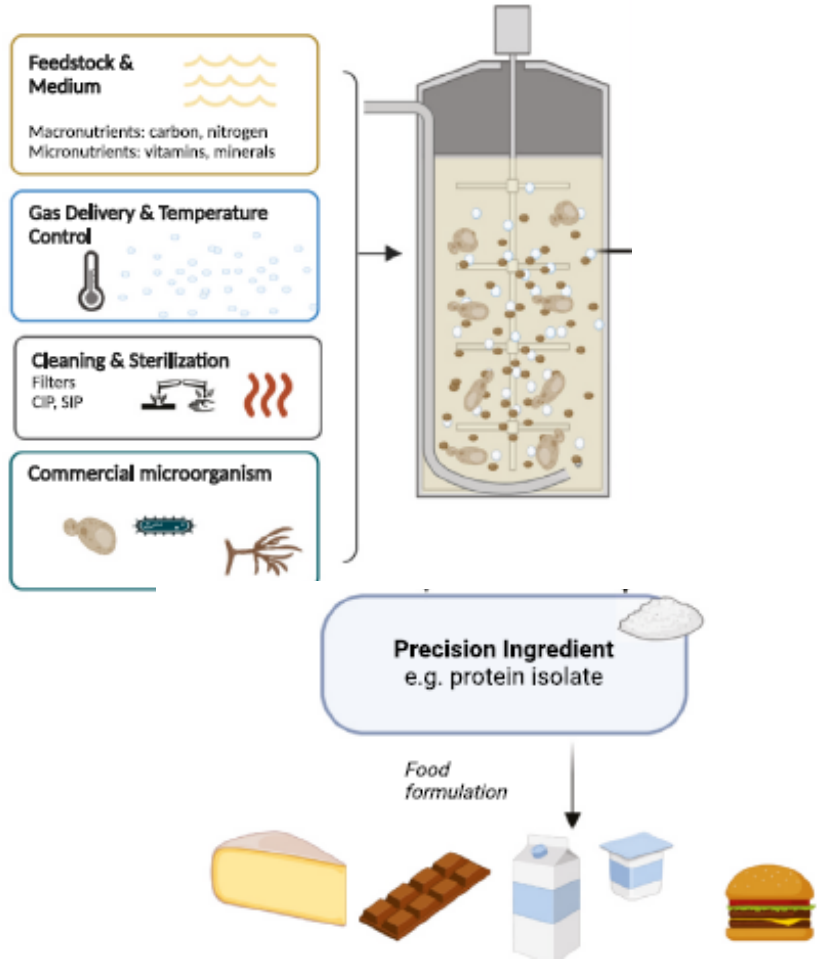
# Background

- Long history of protein consumption.
- FDA has a long history of evaluating the safety of proteins.
  - Bakers yeast protein and modified cottonseed products (1970s)
  - Recombinant chymosin (1990)
  - Mycoprotein (2002)
- Increased interest recently (2013-current)
  - Potato protein isolates,
  - Barley and rice protein isolate,
  - Soy leghemoglobin
  - (etc.)




Adapted from: Eastham & Leman,
Curr Op Food Science, 2024, 58:101194

# Background

- Alternative protein products are a spectrum of products
  - Traditional plant proteins
  - Fungal proteins
  - Precision fermentation products
  - Plant molecular farming products
  - Whole foods from plant biotechnology
  - Animal cell culture

- We have programs that can accommodate all these products.

# Pre-market engagement

Our regulatory processes typically begin with pre-submission meetings.

This is some of our most valuable work

- Developers receive scientific and regulatory suggestions from FDA.
  1. Ensures products are directed to the most appropriate program,
  2. Makes the regulatory process more predictable, and
  3. Identifies potentially unsafe products very early in development providing public health protection and efficient use of developer resources.

# Pre-market engagement

- Two use cases:
  - Purified ingredients
    - New uses of traditional ingredients/foods
    - Precision fermentation products
    - Molecular farming products
  - Whole foods
    - Plant biotechnology
    - Human food from cultured animal cells

# Purified ingredients

Proteins can have a wide range of intended uses in food

- Macro ingredients
  - Protein used as a significant nutrient source
- Processing aids
  - Little, if any, of the protein present in the final food.

Weight-of-evidence approach is used to assess safety.

- This approach takes into account…
  - the identity (source, history of use in food) and intended use of the protein.
- Provides flexibility to ensure the appropriate analyses are performed for the substance and use being evaluated.

# Purified ingredients

- We consider factors such as:
  - Source of the protein
  - Protein type and family—does it raise a potential concern?
  - Dietary intake level
  - Biological function (mode of action)
  - Amino acid sequence comparison with known allergens and toxins
  - *In vitro* digestibility in simulated gastric fluid
  - Oral toxicity studies (often acute or short term tox studies)
  - Additional studies as warranted

**FDA GRN Inventory**

# Purified ingredients

- Animal studies
  - We support efforts to replace, reduce and refine animal studies when supportable by the science. For protein evaluations we request them when warranted based on the existing data and information.
  - Many, many proteins are routinely safely consumed and that generally the proteins/sources known to be harmful are well known (e.g., toxins and allergens).
  - Acute toxicity studies in animals have sometimes been an element of the weight-of-evidence approach.
  - In our view, animal studies should be performed on a case-by-case basis when dictated by protein function or other evidence (e.g., in silico analysis).

# Whole foods - plants

- Comparative approach
    - Described by Codex Alimentarius Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants
    - Compare the safety of new foods to those with a history of safe use.

- Generally assume 100% replacement with conventional counterpart.
    - Three components
        - Molecular characterization to define the nucleic acid change
        - Safety of newly expressed substances
        - Compositional analysis of key nutrients, anti-nutrients and toxicants

- Goal is to assess whether the new food is as safe as comparable food
    - If we concluded it were not as safe as comparable food a risk assessment process would be warranted.

# Whole foods (plants)

- Allergenicity
  - Significant difference between use of a protein as a purified ingredient versus use of a protein as a component of a commodity crop.
  - Purified ingredients are typically used in foods that include a product label where allergens can be declared.
  - In contrast, it would be challenging to label a whole food in a way that identifies new or unexpected allergens in the food.
    - Corn is a fungible commodity where many varieties are routinely commingled as part of typical agricultural practices.
  - For whole plant foods it is especially important that we ensure any new proteins are unlikely to be allergens.

# Human food from cultured animal cells

- FDA conducts premarket consultations to evaluate:
  - Production materials, processes, and manufacturing controls
  - Initial tissue collection
  - Development and maintenance of cell lines and banks
  - Proliferation and differentiation of cells through the time of harvest
  - Components and inputs
- FDA's evaluation focuses on the properties of the harvested cell material that are relevant for safety, including the potential for unlawful food additives and other adulterants
- FDA will engage with USDA on consultations involving livestock and poultry cell lines and share the results of consultations.

# Food from cultured animal cells

- In the context of the completed consultations, FDA considered:
  - Cell sourcing, cell species identity, cell modifications, cell line stability, differentiation
  - Cell bank generation
  - Detailed description of production process and material inputs, including information on safety, regulatory status of media inputs
  - Stepwise hazard analysis with rationale for potential hazards (i.e., chemical, biological, physical) and preventive controls employed
  - Characterization and composition of the harvested cell material and how it compares with a conventional comparator along with proposed specifications
  - Conclusions about safety of the harvested cell material
  - Supplemental and corroborative confidential, commercial or trade secret information placed in separate appendices

# Background

- We recognize and appreciate the recent interest in identifying new or alternative protein sources.

- While FDA supports innovation in food including new protein sources, we must ensure that new, innovative products are safe.

- Increased transparency of our assessment of ingredients in the food supply is part of our approach to enhance food chemical safety.

# Conclusions

- Innovations in science and technology continue to generate new ways of producing food.
  - e.g., precision fermentation, plant molecular farming, animal cell culture
- FDA combines long-standing authorities with policy and scientific knowledge to regulate food safety.
  - This approach is flexible and adaptable to a wide variety of new food production technologies.
- We recognize that new proteins and new technologies will bring new challenges. We are confident that our science-based approach will enable appropriate flexibility to ensure food safety.

# Resources

- Food Ingredients & Packaging | FDA

- Contacts:
  - premarkt@fda.hhs.gov
  - plantbiotech@fda.hhs.gov
  - animalcellculturefoods@fda.hhs.gov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