Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Human Foods Program
U.S. Food and Drug Administration
Docket No. FDA-2026-N-2047

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Wi-fi: FDA-GUEST

OPENING REMARKS

Kyle Diamantas, J.D.
Deputy Commissioner for Human Foods and Senior Counselor to the Secretary

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 1:
The scope of the phrase “dietary substance for use by man to supplement the diet by increasing the total dietary intake” as used in DSHEA

Moderator: Cara Welch, Director, Office of Dietary Supplement Programs, Human Foods Program, FDA

Panelists:
1.1 Jensen Jose, Regulatory Counsel, Center for Science in the Public Interest
1.2 Daniel Fabricant, Ph.D., CEO and President, Natural Products Association

The scope of the phrase “dietary substance for use by man to supplement the diet by increasing the total dietary intake” as used in DSHEA

Cara Welch, Ph.D.
ODSP Director

Friday March 27, 2026

Dietary Ingredients as listed in DSHEA

FD&C Act Sec 201(ff) The term "dietary supplement" —

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

Working Definition

- Sec 201(ff)(1)(E): Dietary Substance
  - "Dietary substance for use by man…"
    - A substance that is commonly used as human food or drink
  - "…to supplement the diet by increasing the total dietary intake"
    - further evidence it is intended to mean foods and food components that humans eat as part of their usual diet
  - Use as a dietary supplement doesn't make something a dietary substance

Public Meeting to Discuss Responsible Innovation in Dietary Supplements

May 16, 2019

- **Session 1: The scope of dietary ingredients under DSHEA**
- **Session 2: Understanding exceptions to the NDIN requirement**
- **Session 3: Comparative perspectives from other regulatory systems**
- **Session 4: Promoting compliance with the NDI notification requirement**
- **Session 5: Open public comment**

Commentary from 2019

DSHEA envisioned a dynamic dietary supplement market with a role for innovation

If "dietary substance" only includes substances already present in foods, then nothing new can get in under this prong

The exact wording that is used in the statutory language is important

It's time to modernize the approach to synthetic compounds that are used in dietary supplement product regardless of their source

"Nutritional Dietary substance…"

As legislation goes, DSHEA is relatively short, but its provisions are there for a reason

Public Meeting Exploring the Scope of Dietary Supplement Ingredients

March 27, 2026

- **Session 1: The scope of the phrase "dietary substance for use by man to supplement the diet by increasing the total dietary intake" as used in DSHEA**
- **Session 2: New methodologies to produce existing dietary ingredients**
- **Session 3: Identity attributes for ingredient types such as proteins, enzymes, and microbials**
- **Session 4: Open public comment**

Session 1 Goals

- Panel makeup
  - Jensen Jose, Center for Science in the Public Interest
  - Daniel Fabricant, Natural Products Association
- Meaning of the phrase “dietary substance for use by man to supplement the diet by increasing the total dietary intake”
- How emerging ingredient types fit within the dietary supplement framework

Questions

Does the source of a dietary substance matter?

Does "dietary substance" include substances that have never been part of the human diet?

Does it matter if a substance is both naturally present in foods and also present as environmental contaminants?

Can any ingredient be a dietary supplement? Are there limits to what the category encompasses?

Does this provision depend on the production method?

What happens when you produce existing dietary ingredients in a new environment?

Potential

- Ensuring robust safety oversight
- Removing unnecessary barriers to innovation
- Statutory language
  - a dietary substance for use by man to supplement the diet by increasing the total dietary intake


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MEETING | MIXED

Public Meeting Exploring the Scope of Dietary Supplement Ingredients

MARCH 27, 2026

Session 1: The scope of the phrase "dietary substance for use by man to supplement the diet by increasing the total dietary intake" as used in DSHEA

Jensen N. Jose, JD
Senior Regulatory Counsel
Center For Science in the Public Interest

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Your Food and Health Watchdog

Question Posed by FDA:

Should “dietary substance” include substances that were never part of the diet?

Public Feedback Questions

1. What is your view on whether the phrase “dietary substance for use by man to supplement the diet by increasing the total dietary intake,” as used in DSHEA, can include substances that have never been part of the diet?

https://www.fda.gov/media/191569/download

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Legislative Intent: Industry View

- **Israelson** (United Natural Products Alliance (UNPA)):
  - “the Conversation comes down to the definition.”
  - “DSHEA was intended to be expansive.”

- **Ventura** (Council for Responsible Nutrition (CRN)):
  - “[CRN] will urge the agency to stay faithful to DHSEA’s intent”
  - “Our longstanding position is that ‘dietary substances’ are not limited to ingredients with prior use in conventional food, but include a wider range of innovative substances”

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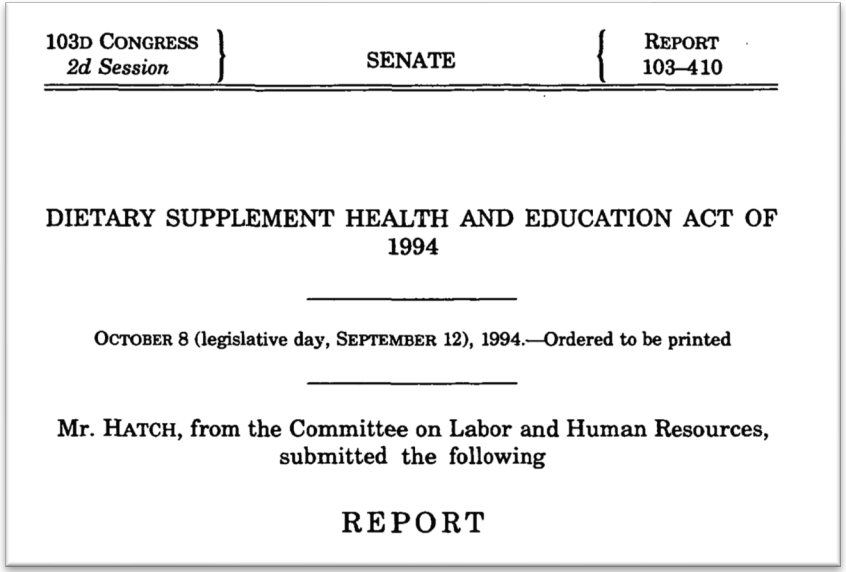
Legislative Intent: Senate

"[E]ncompass those substances which have been isolated from the food supply"



103D CONGRESS
2d Session

SENATE

REPORT
103–410

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

OCTOBER 8 (legislative day, SEPTEMBER 12), 1994.—Ordered to be printed

Mr. HATCH, from the Committee on Labor and Human Resources, submitted the following

REPORT

Senate Committee Report. *DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994,* 103 S. 103 S. Rpt. 410. *P.* 34.

P. 34:

- "The definition is intended to encompass all those substances and materials that are presently contained in dietary supplements as well as substance derived from foods."
- "This last section is meant to encompass those substances which have been isolated from the food supply and are being provided to increase the total dietary intake by supplementing the diet."

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Legislative Intent: Senate

SECTION 3. DEFINITION OF DIETARY SUPPLEMENT; EXCLUSION FROM DEFINITION OF DRUG OR FOOD ADDITIVE

Section 3 amends the act to add a new paragraph (ff) which for the first time defines dietary supplement. First, a dietary supplement must be a product "intended to supplement the diet by increasing the total dietary intake". The definition is intended to encompass all those substances and materials that are presently contained in dietary supplements as well as substance derived from foods. Thus, a dietary supplement must bear or contain one or more of a vitamin, a mineral, an herb or other botanical, or amino acid or another dietary substance for use by man to supplement the diet by increasing total dietary intake.

This last section is meant to encompass those substances which have been isolated from the food supply and are being provided to increase the total dietary intake by supplementing the diet. In addition, concentrates, metabolite, constituents, extracts, or combinations of the items previously described may be included in a dietary supplement.

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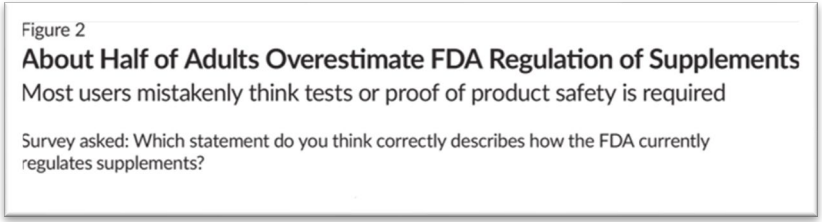
Senate Committee Report. *DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994,* 103 S. 103 S. Rpt. 410. *P.* 34. https://plus.lexis.com/api/document/collection/statutes-legislation/id/3SWR-X570-0001-V3DC-00000-00?cite=103%20S.%20Rpt.%20410&context=1530671.

Consumers' Belief v. Trust

Loren Israelson (UNPA):



Pew Charitable Trusts (May 19, 2021)
https://www.pew.org/en/research-and-analysis/fact-sheets/2019/12/americans-support-requiring-supplement-makers-to-tell-fda-about-their-products

> 48% believe dietary supplements are regulated by the U.S. government, with most consumers incorrectly assuming they are regulated the same as prescription or over-the-counter (OTC) drugs.

Consumer Health Product Association (Jun 3, 2025)
https://www.chpa.org/news/2025/06/us-voters-demand-action-new-survey-finds-strong-support-dietary-supplement-reform-0

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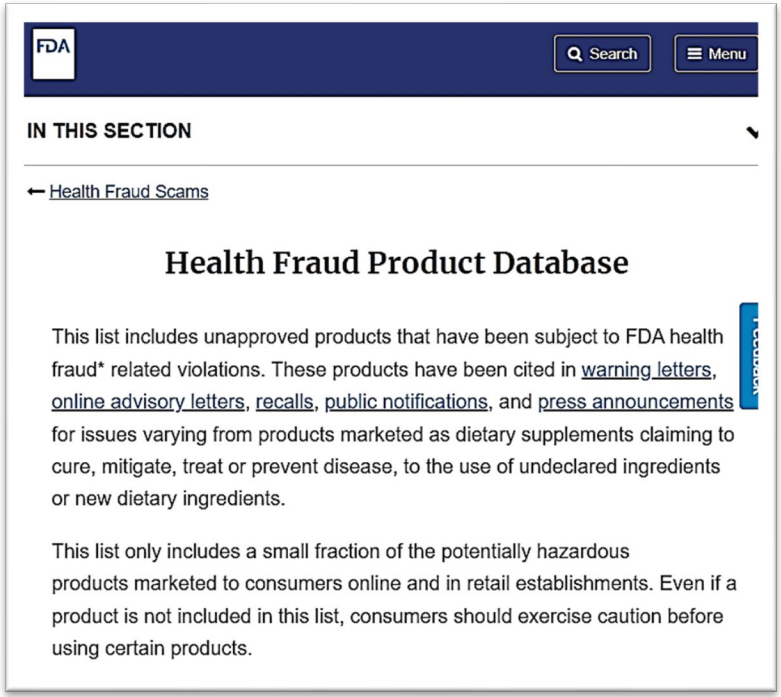
Dietary Supplements are a Minefield

CDPH Issues Second Consumer Warning Not to Take Pyramid Wholesale Sexual Enhancement Supplements

April 9, 2024
NR24-009
Contact: media@cdph.ca.gov

Additional products discovered to contain undeclared prescription drugs that may cause illness, injury, or death

https://www.cdph.ca.gov/Programs/OPA/Pages/NR24-009.aspx



FDA Search Menu

IN THIS SECTION

← Health Fraud Scams

Health Fraud Product Database

This list includes unapproved products that have been subject to FDA health fraud* related violations. These products have been cited in warning letters, online advisory letters, recalls, public notifications, and press announcements for issues varying from products marketed as dietary supplements claiming to cure, mitigate, treat or prevent disease, to the use of undeclared ingredients or new dietary ingredients.

This list only includes a small fraction of the potentially hazardous products marketed to consumers online and in retail establishments. Even if a product is not included in this list, consumers should exercise caution before using certain products.

2,147 entries (3/26/26)

https://www.fda.gov/consumers/health-fraud-scams/health-fraud-product-database

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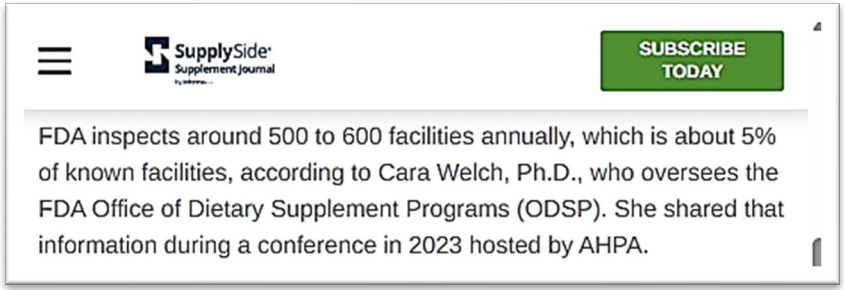
Expanding Scope is Deregulation

Dietary supplement companies are currently:

- Not required to disclose proof of safety (GRAS)
- Not required to disclose proof of effectiveness (Substantiation)
- Rarely inspected (<5%)

Now, dietary supplement companies:

- Don't want to show their ingredients are in the diet



https://www.supplysidesj.com/supplement-regulations/fda-increases-annual-domestic-foreign-dietary-supplement-inspections

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Concerns with Expanding Scope:

Exposing Consumers against the "Charlatans"& Stifling Drug Innovation

The New York Times

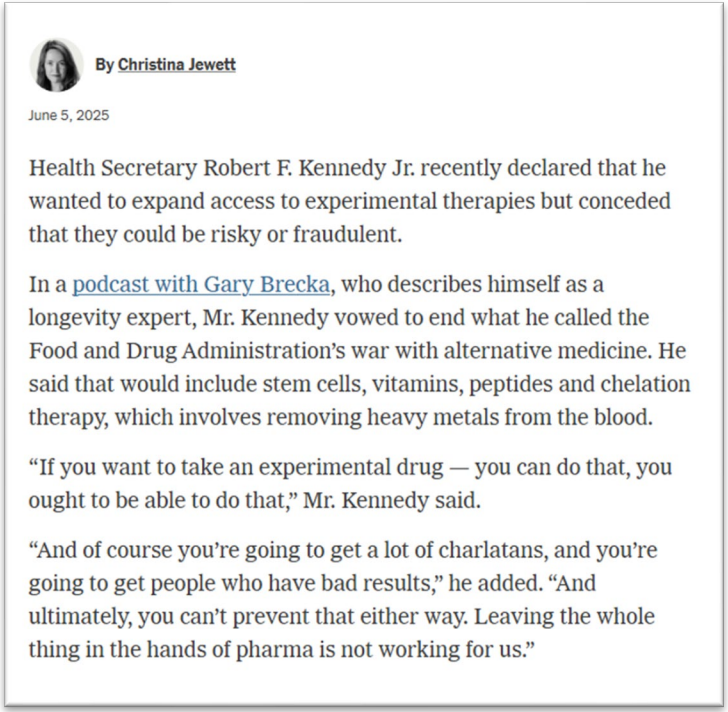
GIVE THE TIMES

U.S. Health Policy | Inside the C.D.C. | Adviser Quits Vaccine Panel | Covid Vacci

Kennedy Says 'Charlatans' Are No Reason to Block Unproven Stem Cell Treatments

The U.S. health secretary said people should have access to experimental therapies including unregulated uses of stem cells. But some methods have resulted in blindness, tumors and other injuries.

https://www.nytimes.com/2025/06/05/health/kennedy-stem-cells-experimental-treatments.html



By Christina Jewett

June 5, 2025

Health Secretary Robert F. Kennedy Jr. recently declared that he wanted to expand access to experimental therapies but conceded that they could be risky or fraudulent.

In a podcast with Gary Brecka, who describes himself as a longevity expert, Mr. Kennedy vowed to end what he called the Food and Drug Administration's war with alternative medicine. He said that would include stem cells, vitamins, peptides and chelation therapy, which involves removing heavy metals from the blood.

"If you want to take an experimental drug — you can do that, you ought to be able to do that," Mr. Kennedy said.

"And of course you're going to get a lot of charlatans, and you're going to get people who have bad results," he added. "And ultimately, you can't prevent that either way. Leaving the whole thing in the hands of pharma is not working for us."

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Exposing Consumers Against Unsafe Ingredients

- Through GRAS, any chemical can become a dietary ingredient without FDA knowledge
- Industry will still use GRAS to get ingredients without FDA review

"Historically, FDA has forced industry to take the circuitous route of seeking GRAS status for ingredients first before qualifying as dietary ingredients when a direct route provided by the NDI notification would have been more efficient."

-Jeff Ventura (CRN)

Is FDA opening the long-shut DSHEA 'innovation door'? Opens in new window

23-Mar-2026 by Stephen Daniells

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Expansion of Scope Will Not Fix the Non-Dietary Ingredient Problem

- Non-dietary ingredients put some supplements in regulatory “limbo”
- However, many supplements:
  - include other dietary ingredients
  - fail the definition of dietary supplements due to non-ingredient issues (e.g., labeling)

https://www.cspi.org/resource/letter-fda-re-sales-unapproved-drug-tianeptine

https://www.cspi.org/press-release/fda-urged-crack-down-marketers-illegal-drug-phenibut-supplements-and-other-products

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Recommendations:
Build Consumer Trust in FDA Oversight

- **GRAS**:
  - Require NDINs
  - Require greater disclosure of safety data for GRAS ingredients on the market
- **Claims:**
  - Increase monitoring and enforcement
  - More guidance on Structure/Function Claims and substantiation
  - Require disclosure of evidence supporting claims
- **Drug innovation:** Focus on safety and effectiveness of evidence-based medicine

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Your Food and Health Watchdog

FDA Public Meeting on Dietary Supplement Innovation and the Scope of Dietary Ingredients

Daniel Fabricant, Ph.D.
CEO/President
March 27, 2026
Daniel.Fabricant@npanational.org

DSHEA works, including twin pillars of giving FDA tools to protect consumers from harmful products and promoting wide access to supplements. No need for major statutory overhaul. The law allows for flexibility in technological ingredient advances and industry growth.

Address dietary supplement definition issue in DSHEA, “dietary substance for use by man to supplement the diet by increasing the total dietary intake." This is open for broad interpretation, consistent with the intent of Congress to promote broad consumer access to safe supplements that promote health.

Future of industry. Address three pillars:

(A) Need for definitional flexibility (B) Clarity/reform of drug preclusion clause (C) Preemption of state/local laws and need for uniform federal regulatory framework so FDA can effectively do its job.

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 1:
Q&A

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Currently on break

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 2:
New methodologies to produce existing dietary ingredients

Moderator: Phil Yeager, Director of Research and Evaluation, ODSP, HFP, FDA

Panelists:

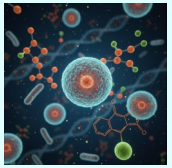
2.1 Weslee Glenn, Vice President of Innovation, Ayana Bio
2.2 Duffy MacKay, Sr VP of Dietary Supplements, Consumer Healthcare Products Association
2.3 John Deaton, VP of Science and Technology, Biohm Technologies
2.4 Tony Pavel, Partner, Keller and Heckman LLP
2.5 Frank Romanski, Global VP of Strategic Growth & Revenue Management, Lonza Capsules & Health Ingredients

Session 2: New methodologies to produce existing dietary ingredients

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

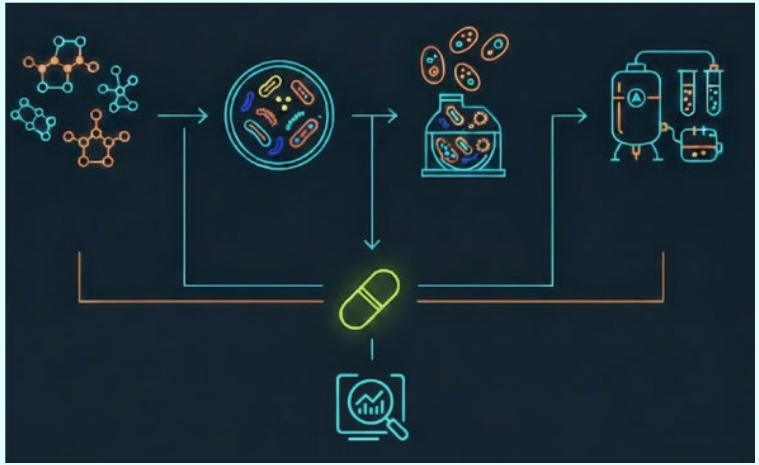
Phil Yeager, PhD, JD, DABT, CHRC
FDA/HFP/OFCSDSI/ODSP Director of Research and Evaluation

Friday, March 27, 2026
College Park, MD



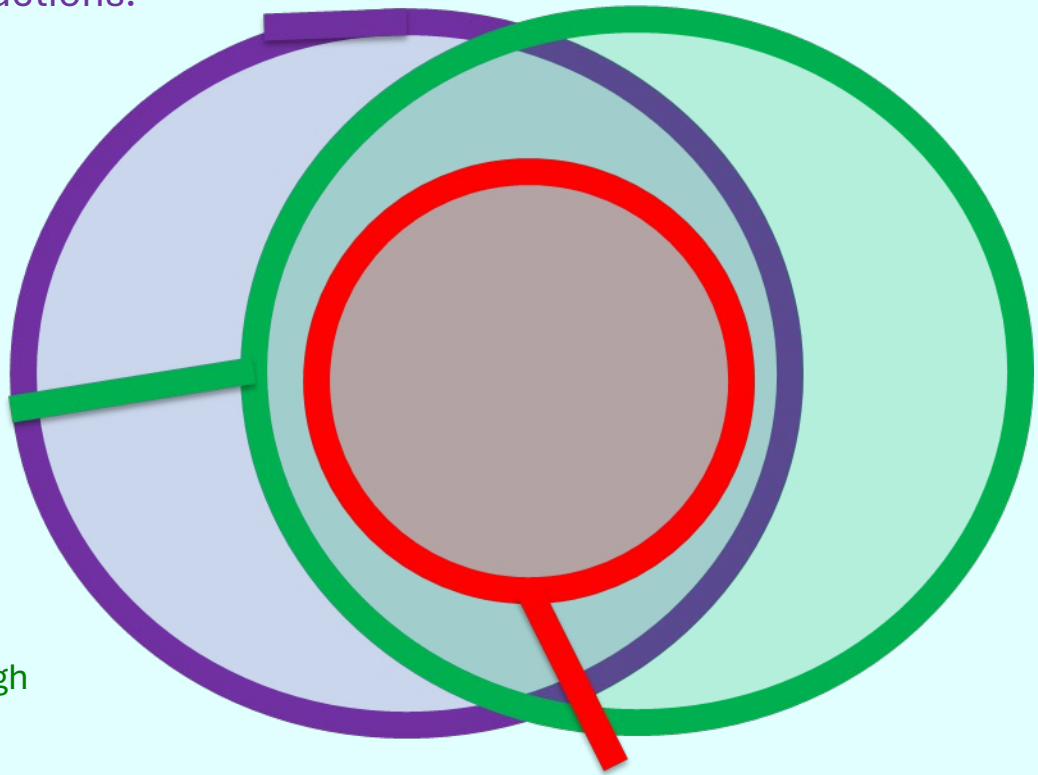
Session 2: New methodologies to produce existing dietary ingredients

This panel will discuss production technologies that are being applied to the science of dietary supplements, including **synthesis**, **precision fermentation**, **cell culture technology**, and **recombinant production**, and how these scientific and technical advancements intersect with dietary ingredient production to inform our assessment.



Synthesis: creation of a new compound through chemical reactions.[1]

Cell culture technology: growing cells in a controlled, artificial environment.[2] These can be natural cells or cells that have been genetically modified using recombinant technology to produce something through precision fermentation.

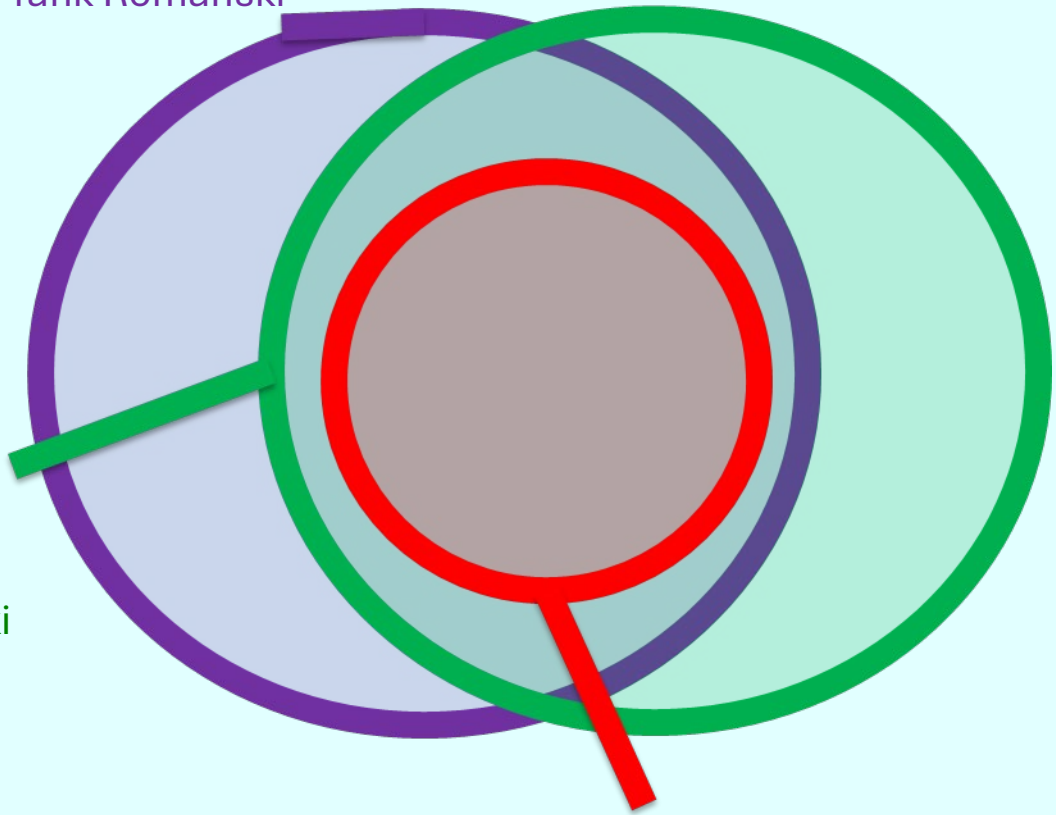


Production Technologies Relevant to Dietary Supplements

1 Merriam-Webster Dictionary
2 NCI Dictionary of Cancer Terms https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cell-culture (The growth of microorganisms such as bacteria and yeast, or human, plant, or animal cells in the laboratory)
3 https://gfi.org/fermentation/; https://www.genome.gov/genetics-glossary/Recombinant-DNA-Technology

Precision fermentation/recombinant production: Genetic modification of yeast, fungi, or other bacteria to be a cell factory and produce specific ingredients. (focus: recombinant production focuses on the upstream changes to the organism's DNA, while precision fermentation focuses on the downstream fermentation of the modified organism to produce the final product).[3]

Synthesis: Weslee Glenn, Duffy MacKay, John Deaton, Tony Pavel, Frank Romanski



Cell culture technology: Weslee Glenn, Duffy MacKay, John Deaton, Tony Pavel, Frank Romanski

Production Technologies Relevant to Dietary Supplements

Precision fermentation/recombinant production: John Deaton, Tony Pavel, Weslee Glenn (endogenous)

Session 2 Theme: How different methodologies impact the characteristics or attributes of an ingredient.

What characteristics can equate or distinguish an ingredient made by different methods?

What analytical information is sufficient to characterize these attributes?

What level of modification of a dietary substance creates a new ingredient?

What level of modification of a dietary substance creates a new ingredient?

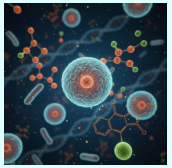
What analytical information is sufficient to show that production organisms, residual components, or unexpected byproducts has been sufficiently removed from a proposed NDI?

What attributes distinguish ingredients produced through precision fermentation or cellular agriculture from their naturally occurring counterparts? *

What role should the production organism's regulatory status (e.g., GRAS, food additive approval) play in determining whether the fermentation-derived ingredient qualifies as a dietary substance?

What attributes distinguish synthetic or recombinant versions of biological molecules (e.g., peptides, proteins, enzymes) from their naturally occurring counterparts?

***e.g., explanation of the modification to production organism, sequencing information, information on the identity of the production organism, purification process**



Session 2: New methodologies to produce existing dietary ingredients

2.1 Weslee Glenn, Vice President of Innovation, Ayana Bio
2.2 Duffy MacKay, Senior Vice President of Dietary Supplements, Consumer Healthcare Products Association (CHPA)
2.3 John Deaton, Vice President of Science and Technology, Biohm Technologies
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AYANA BIO

Moving beyond “harvest and fix” with plant cell culture

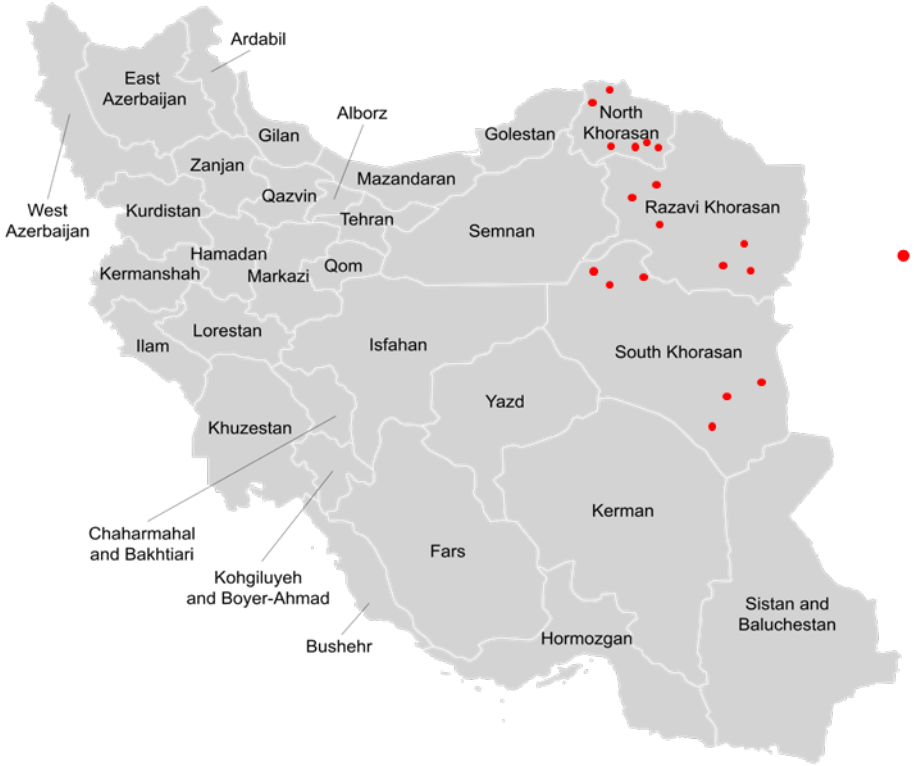
Weslee Glenn, Ph.D.
VP of Innovation
March 27, 2026

FDA - ODSP

- www.ayanabio.com

Botanical ingredients are mostly made in two ways

botanical products (like saffron) vary by region...



• Study Harvest Sites

...even ones near each other

But data can teach us the determinants

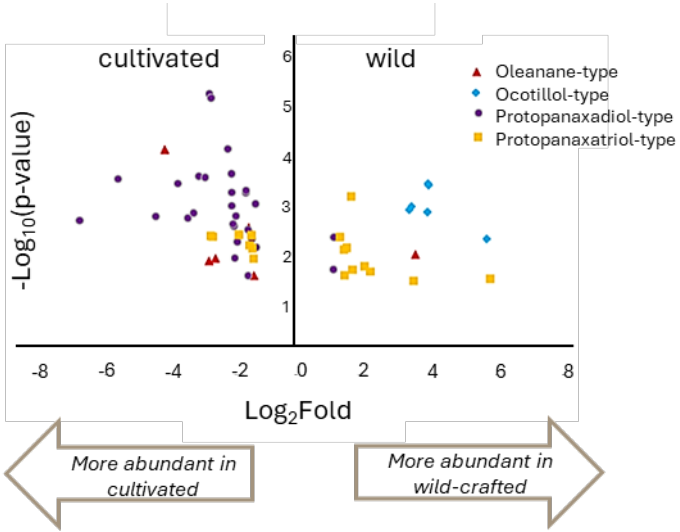
Location Village	Flower Yield gm-2	Stigma Yield gm-2	Crocin Content percent (%)	Altitude (m.a.s.l)	Relative Humidity (%)	Winter High Temperature (°C)	Summer High Temperature (°C)	Number of Annual Frost Days days	Average Annual Temperature (°C)	Average Annual Rainfall mm
Shirvan	0.80	0.091	59.8	1168.33	60	25.2	41.6	107	13.1	226.7
Faruj	0.78	0.092	54.9	1207.33	57	23.0	41.5	89	12.6	243.6
Zavareh	0.69	0.081	63.9	1370.33	45	24.0	41.0	89	14.5	245.0
Torbat-e Heydarieh	0.83	0.098	69.3	1323.33	45	24.6	40.6	88	14.3	246.2
Ghayen	0.63	0.081	52.3	1768.33	40	27.2	42.0	88	14.7	161.0
Birjand	0.79	0.090	39.9	1812.66	35	21.5	43.0	71	16.5	147.4

	Flower Yld	Stigma Yld	[Safranal]	[Picrocrocins]	[Crocins]
Relative Humidity	0.25	0.28	0.18	0.22	0.31
Winter High Temp	-0.38	-0.21	-0.27	0.05	0.29
Summer High Temp	-0.37	-0.55	-0.12	-0.55	-0.70
No. Frost Days	0.04	0.02	0.04	0.22	0.43
Avg annual Temp	-0.12	-0.15	-0.09	-0.25	-0.38
Avg annual Rain	0.25	0.20	0.19	0.48	0.60

Italian Journal of Agrometeorology (2): 43-55, 2021

Farmed plants ≠ wild-crafted ones

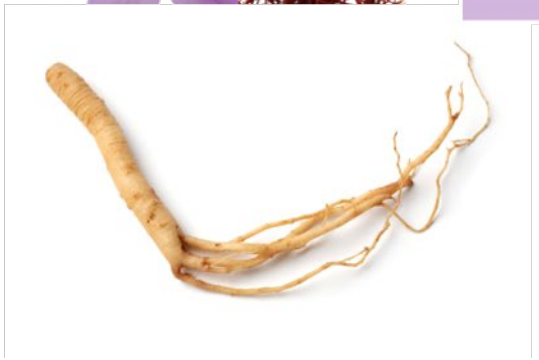
Image Credit: Cornell University



Why?...because growth conditions matter.

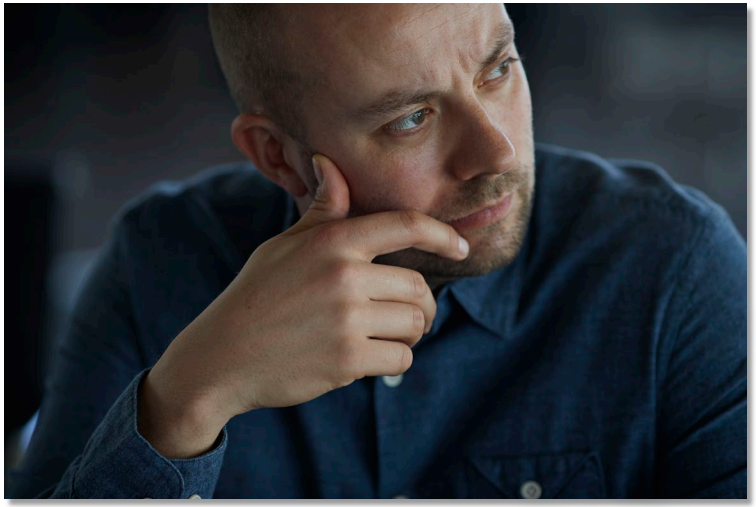
Molecules 2023, 28(1), 9, 10.3390/molecules28010009

“Harvest and fix” tries to correct at the finish line



Solvents, heat, etc.

Itay Dana (Novella), *Why I’m Done With “Harvest and Fix”: The Case for Precision Botanicals*

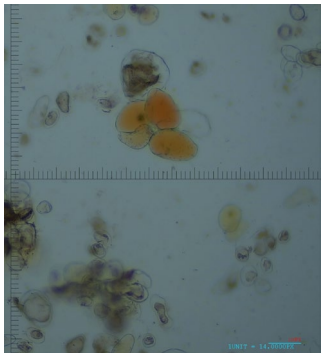


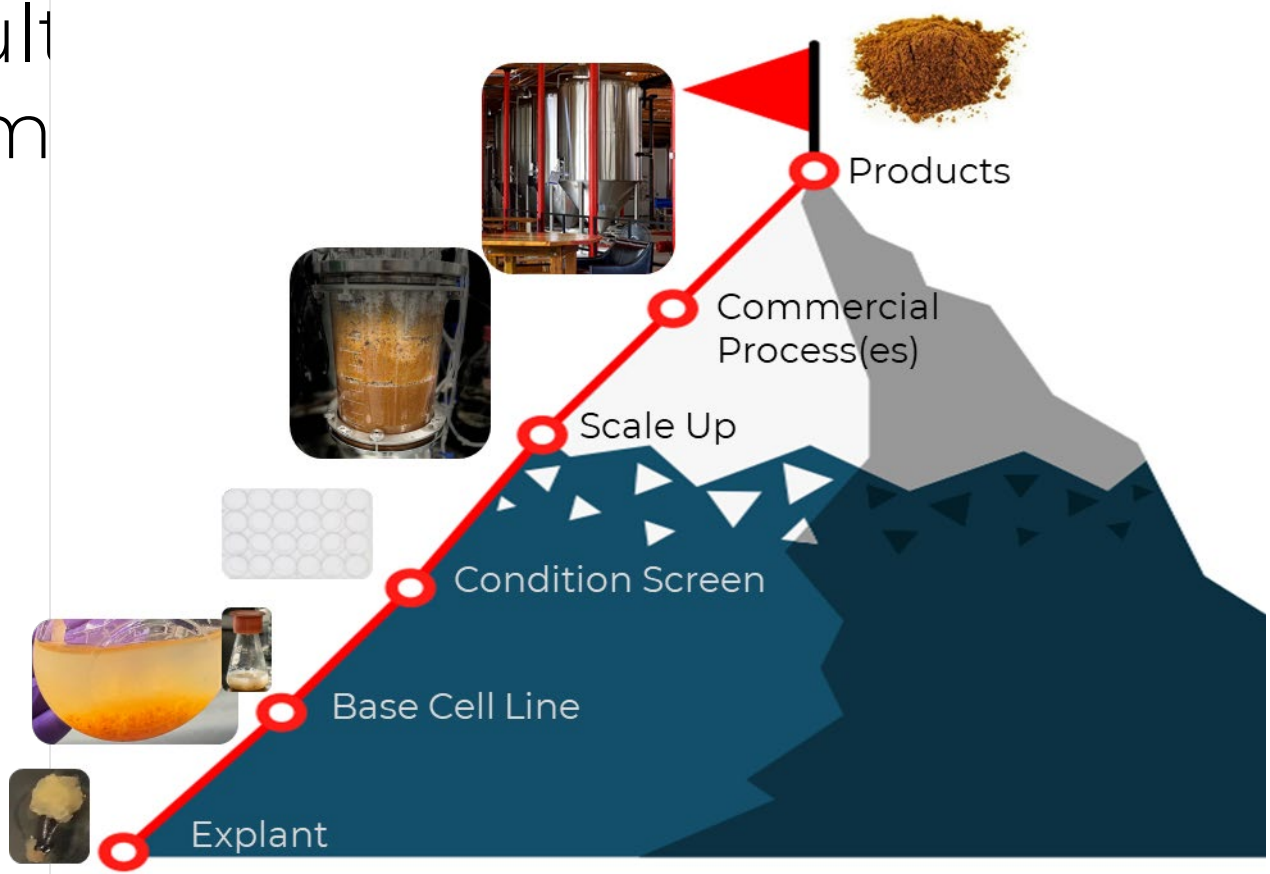
Can we control composition at the start?

Itay Dana (Novella), *Why I'm Done With "Harvest and Fix": The Case for Precision Botanicals*

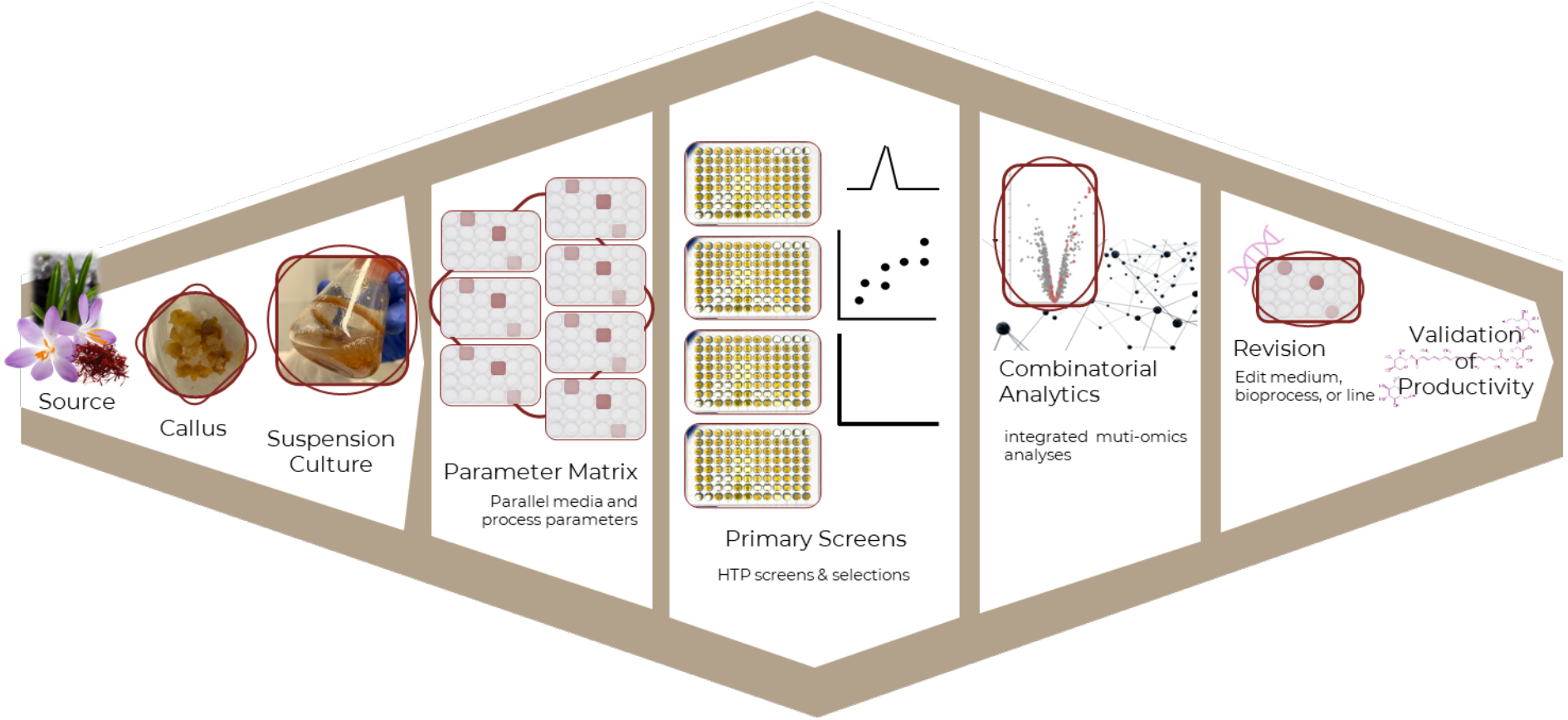
Plant cell culture controls com at the start.

What is it?



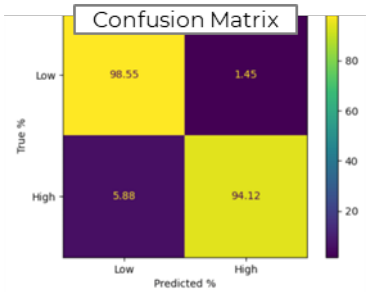


Plant cell culture in the 21st Century



Multi-omics data sets help us predict drivers

Low & High Levels of Phenolic were well predicted by ML model



Low group sample median concentration is almost 10x lower than ***High*** group sample median concentration

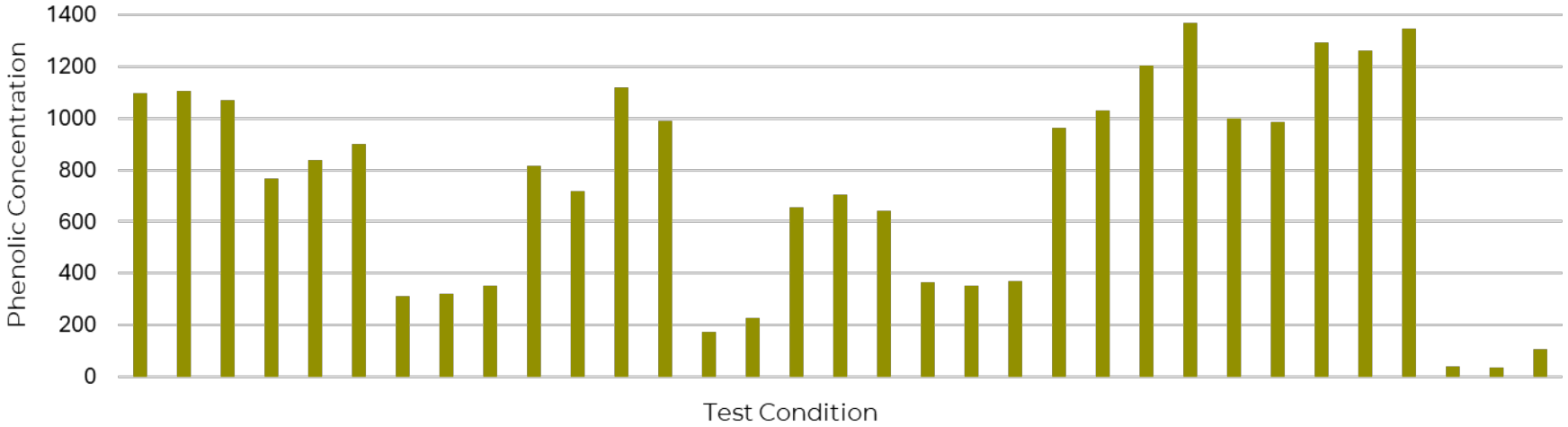
Predictive *High* Concentration Drivers

- Condition 2 (fed signaling molecule 2)
- Condition 3 (fed signaling molecule 3)
- Low volume in vessel

Predictive *Low* Concentration Drivers

- Condition 1 (fed signaling molecule 1)
- Condition 4 (fed signaling molecule 4)
- High volume in vessel

We can improve productivity by using the high drivers and avoiding the low drivers



We controllably produced multiple ingredient compositions from a single line (twice)

AYANA BIO

SAGE

Traditional material known for combination of phenolics and terpenes.

BASIL

Traditional material noted & marketed for high triterpene content. Plant cell cultivation also found to produce relatively higher triterpenes.

How do the technologies compare?

	Wild Crafting	*Modern Farming (Soil)*	*Plant Cell Culture*
Start Date	300,000 BC	1890s	1902
Controllable Biomass?	✗	✓	✓
Defined Inputs?	✗	✗ ✓	✓
Controllable Composition?	✗	✗	✓
On-Demand Production?	✗	✗	✓

Just because it’s grown in the ground…

…. doesn’t mean it is safer.

Just because it’s grown in a tank…

…. doesn’t mean the phytocomplex is novel.

AYANA BIO

THANK YOU

Wes@ayanabio.com

Dietary Ingredients Under DSHEA

Restoring Congressional Intent

Duffy MacKay, ND
SVP, Dietary Supplements, CHPA

201(FF)(1) (E): ENABLES INNOVATION

Congress anticipated future developments and built regulatory flexibility

- **Catch-all language** avoided statutory amendments as science evolved
- Focus on **function** (supplement the diet) and **purpose** (raise total dietary intake), **not source** (part of the usual diet) or **manufacturing** method

DSHEA Supports Innovation

- DSHEA was not intended to prohibit:
  - Advances in science, including new and evolving ingredients (NDI)
  - Manufacturing changes that enhance purity, consistency, and safety
  - More efficient, environmentally responsible manufacturing methods

DSHEA'S INTENDED FLEXIBILITY

Fish Oil/Omega-3 Concentrates

- **Status in 1994:** Natural TG fish oil (20-30% omega-3)
- **Today:** Concentrated, purified EE omega-3 (50-70% omega-3)
- **Relevance:** NDI review focused on safety at **higher intake EPA/DHA**, altered **chemical form**, not whether Ethyl Ester fatty acids were "already in diet"

Phosphatidylserine (PS)

- **Status in 1994:** Bovine derived PS (ODI).
- **Evolution:** BSE concerns – chem/enzymatic synthesis from lecithin, soy/sunflower PS,
- **Relevance:** FDA GRAS notices soy/sunflower PS: same substance; FA profile difference not material to safety.
- PS evolved in **source** and **manufacture,** but **not regulatory status** (identity and CAS ref) or **safety**

MANUFACTURING MODERNIZATION AND REGULATORY CONTINUITY

BALANCING INNOVATION WITH CONSISTENT REGULATORY STANDARDS

THESIS AND REGULATORY CONSISTENCY

Food policy on synthetic vs. natural

- Manufacturing method alone **does not change ingredient identity, safety, or regulatory status.**
- Safety determinations are based on finished ingredient **specifications, impurities, exposure**, **metabolism**, and **safety data**—not whether an ingredient is "natural" or "in the diet" or how its manufactured.

Long-standing FDA acceptance of synthetic versions of botanical constituents (food and supps):

- Synthetic vitamin C vs. citrus-derived ascorbic acid
- Synthetic beta-carotene vs. carrot-derived beta-carotene
- Synthetic fibers vs. plant-derived fibers

Source and manufacture can differ, while identity and biological function do not

FDA GUIDANCE ON MANUFACTURING CHANGES, 2014

FOOD: CHANGES TO MANUFACTURING

GRAS and Chemical Identity

- **L(+)-tartaric acid** as by-product of **wine making** is GRAS affirmed (21 CFR 184.1099)
- **L(+)-tartaric acid** by enzyme-catalyzed **synthesis** is GRAS for same uses
    - meets Food Chemicals Codex (FCC) specifications (chemically identical)

FDA review of synthetic L(+)-tartaric acid

- No new safety concerns; dietary exposure consistent with traditional tartaric acid use.
- Direct Substitute - synthetic form retained same regulatory status (21 CFR 184.1099)

Regulatory Parity – Food and DS

- Tartaric acid is naturally present in grapes and wine = botanical constituent
- **Synthetic Tartaric acid** could be used in **DS** because "present in the food supply as an article used for food in a form in which the food has not been chemically altered".

FDA GUIDANCE ON MANUFACTURING CHANGES 2014

blish the safety of

CHPA

SYNTHETIC DIETARY FIBER

- **Polydextrose**: Synthetic polymer of glucose—**not a natural component of the diet.**
  - Affirmed GRAS for use in foods (21 CFR §184.1444)
  - Used in beverages, baked goods, and **supplements**.
  - **New and synthetic non-digestible carb** eligible as dietary fiber when **safety** and **benefit** are demonstrated.
  - **Safety** based on **chemistry, exposure, composition** of finished ingredient, **metabolism,** and **safety data**—not whether an ingredient is **"natural"** or **"part of the usual diet"**
  - FDA regulatory principles already accepts that **functionally identical** or **improved versions of bioactive compounds** can be **safe** and **lawful**.
    - It is erroneous to exclude this opportunity for synthetic NDI's

A SYNTHETIC BOTANICAL CONSTITUENT IS A DIETARY INGREDIENT SUBJECT TO THE SAME NDI ANALYSIS AND SAFETY STANDARDS AS ANY DIETARY INGREDIENT

Policy Consistency

FDA has previously accepted NDI notifications for synthetic botanical ingredients without objection

- **Synthetic Zeaxanthin** (NDI Report No. 96)
  - Roche Vitamins, Inc. in March 2001

- **Synthetic (-)-hydroxycitric acid** (NDI Report No 35)
  - HOB Ireland, Lt. in January 1999

2016 NDI Draft Guidance – Correction Needed

FDA must align the Final NDI Guidance with DSHEA's plain language, which does not exclude synthetic versions of botanical ingredients from 201(ff)(1)(E)

MANUFACTURING METHOD INFORMS SAFETY ASSESSMENT, BUT DOES NOT PRECLUDE EVALUATION AS NDI

Identity and Safety are Case Specific Evaluations

- Ingredient name
  - chemical name
  - common or
  - trade name
- Applicable ID number
  - CAS Reg. No.
  - Enzyme Commission No
- Chemical formula(e)

- Physical properties
- Chemical properties
  - Specifications for properties
  - E.g., Melting point, boiling point, specific gravity, refractive index, optical rotation, pH, solubility, reactivity, particle size, and chromatographic, spectroscopic or spectrometric data that can be used as a "fingerprint" for identification.

- Source
- Manufacturing Method
- Quantitative composition
- Impurities
- Contaminants
- Potential byproducts

CONCLUSION

- Clause (E) is a **catch-all** for novel ingredients not contemplated in 1994
  - **Not** intended as a **barrier to innovation**
  - Defined by **function** and **purpose**, not source or manufacturing method
- If a new or novel ingredient is:
  - Intended to **supplement the diet**
  - Intended for **ingestion in supplement form(s)**
  - Affect the **structure and function of the body**
  - Has **not** been investigated or approved as a **drug** (IND preclusion - race to market provisions)
- FDA should **evaluate as an NDI,** regardless of manufacturing method or relation to traditional diet
  - Manufacturing method and source **inform safety assessment**, but does **not preclude evaluation as NDI**
- **GRAS** process should **not** serve as a **roundabout mechanism** for establishing the **safety** of ingredients intended for **dietary supplements.**

CHPA

Thank You!

Dietary Ingredients Under DSHEA

Restoring Congressional Intent

Duffy MacKay, ND
SVP, Dietary Supplements CHPA
dmackay@chpa.org

Production of Enzymes for Food and Beverage applications

John Deaton PhD
VP of Science & Technology
Biohm

1854-1922

Dr. Jokichi Takamine

- **1894:** Patented the first process for the industrial production of an enzyme – Fungal Amylase

- The product became known as TakaDiastase from Aspergillus oryzae. The first digestive enzyme!

  - Licensed the marketing rights for Takadiastase, mixed with peppermint, as a digestive aid to Parke, Davis Co.

- Discovered "adrenalin" from animal glands – Today it is called epinephrine.

- Emigrated to NYC in 1894, set up his own laboratory (Takamine Labs).

Types of Hydrolase Enzymes

Carbohydrases

- Amylases
  - Pancreatic
  - Malt
  - Bacterial
  - Fungal
- Cellulases and Hemicellulases
- Pectinases
- Other carbohydrases (lactase, invertase, β-galctosidase, α-galactosidase)

Proteases

- Animal (Pancreatic, pepsin, trypsin)
- Plant (bromelain, papain, ficin, malt)
- Bacterial
- Fungal

Lipases / Esterases

- Pancreatic
- Bacterial
- Fungal

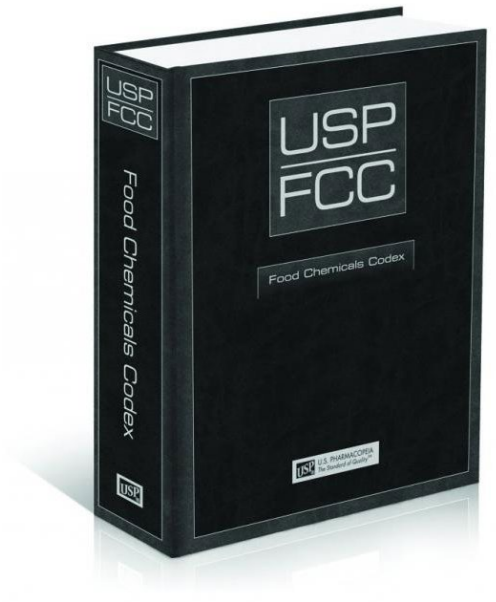
Activity

- Activity for the most part can be defined as a measurement of potency. It is tested against time under specific controllable conditions.

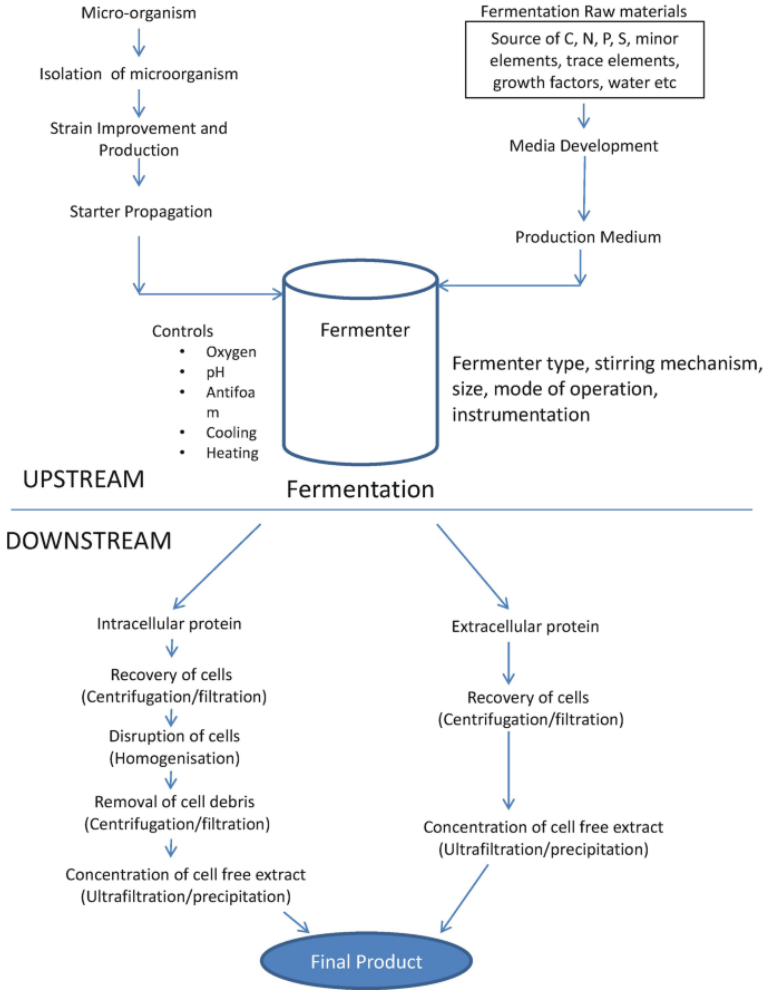
- The chemical composition of the active and inactive enzyme is the same.

- FCC (or USP) assays methods

- Exceptions are made when no such assay exists or if another assay unit is more familiar in the marketplace (i.e. Bromelain FCC: PU / Marketplace: GDU).



PRECISION FERMENTATION PROCESS



PRECISION FERMENTATION PROCESS

Upstream

Target selection
E.g., protein, lipid, pigment, vitamin

Host selection & strain development
Host is selected for target expression and strain functionality is optimized

Feedstock selection
E.g., sugar or industry side streams depending on host strain and target

Fermentation

Fermenter design
Submerged, solid-state, or membrane cell-recycle bioreactor

Process optimization
pH, temperature, oxygen (or no oxygen), concentration of salt

Downstream

Pre-treatment

Separation

Concentration

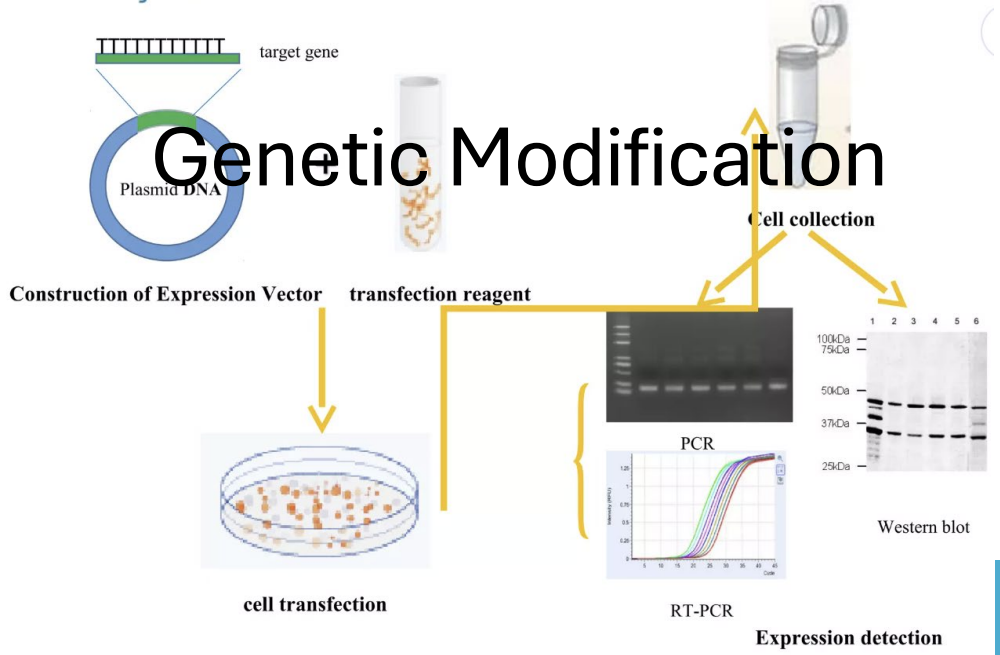
Purification

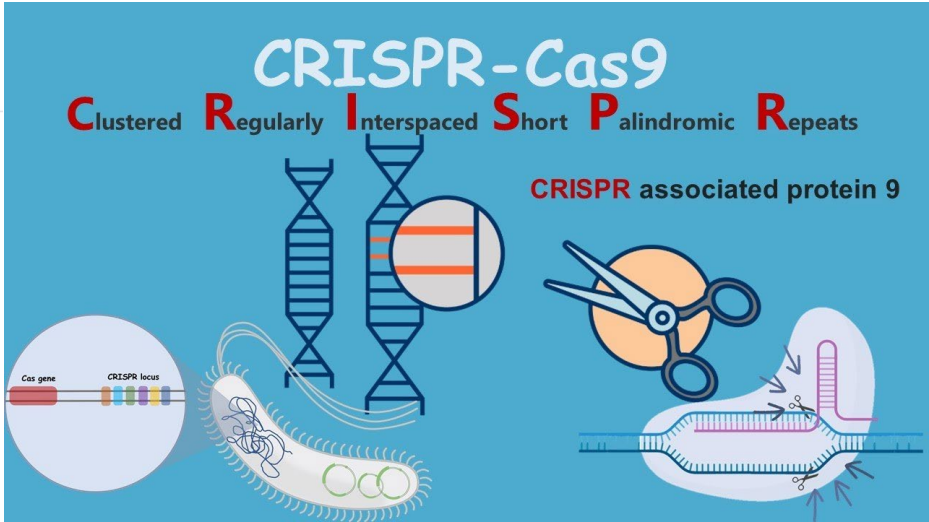
Product formulation

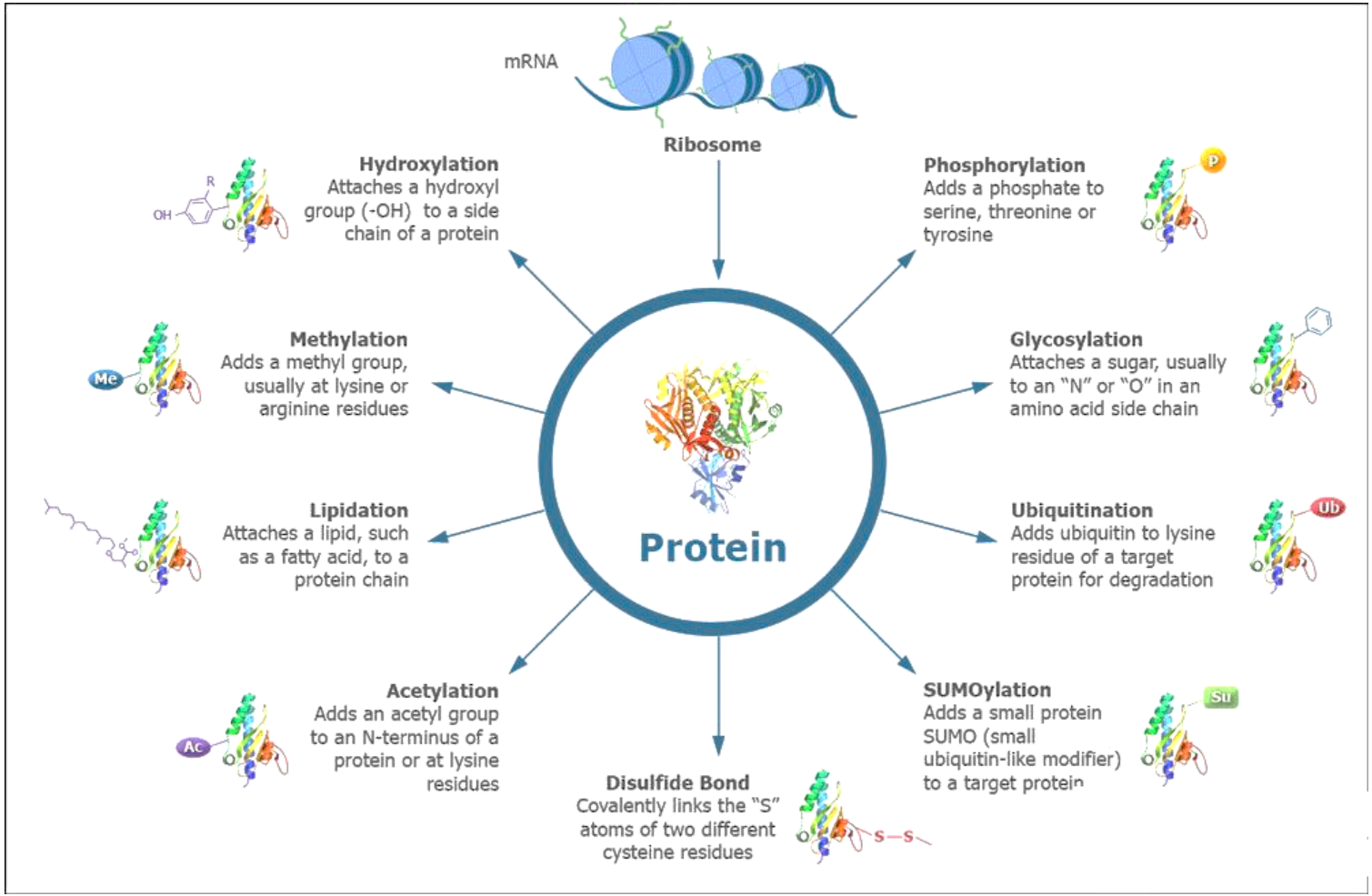
FERMENTATION

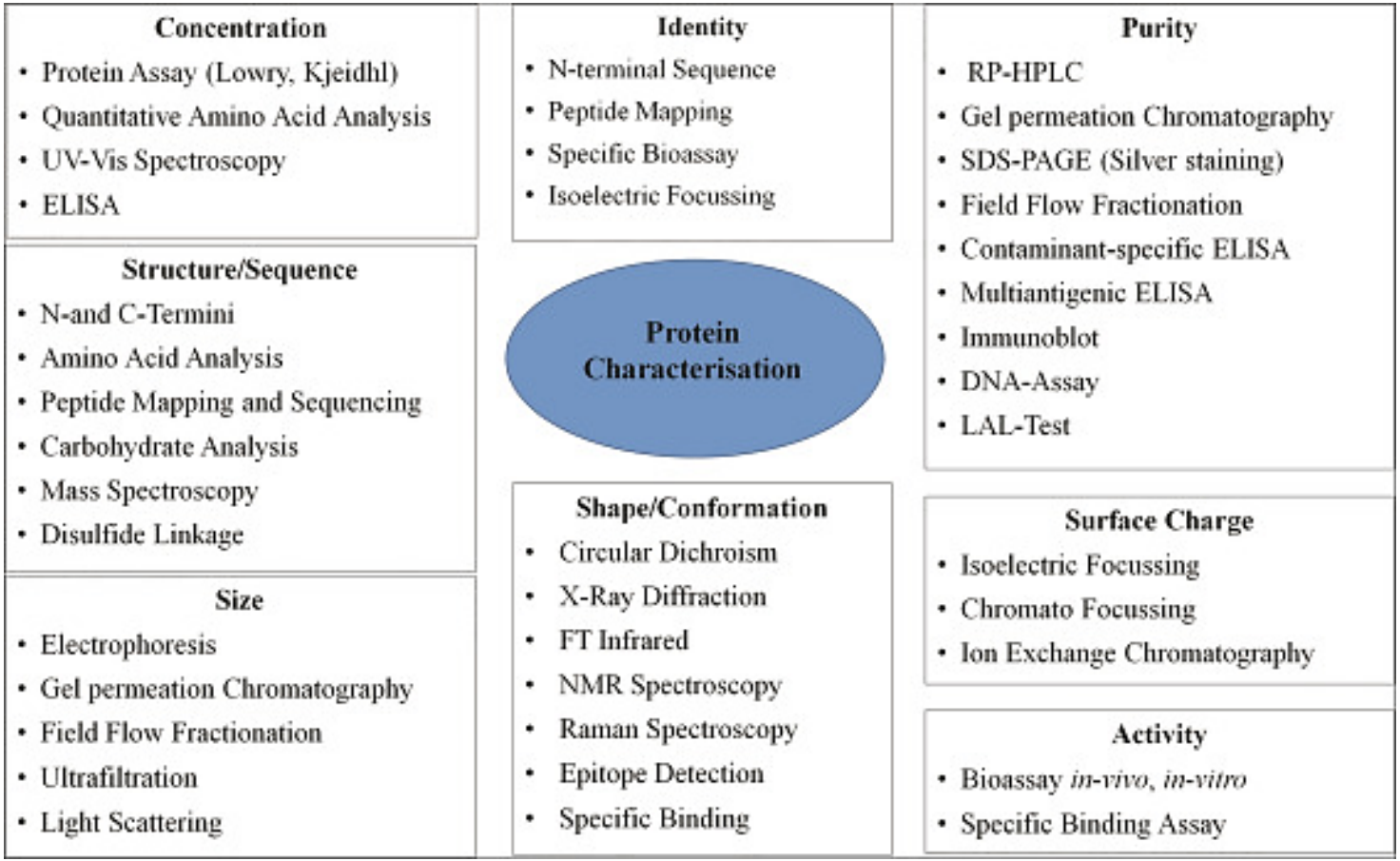
TYPES	 Traditional	 Biomass	 Precision
Short definition	**Microbes** under anaerobic conditions **convert sugars into end-products** with unique texture or flavor properties.	Use of **rapid growth microbes** to efficiently **produce large amounts** of protein rich biomass.	**Precisely designed microbes to produce specific functional ingredients**.
Key features	• Native or starter microbial cultures present in the final product • Uses traditional high-value raw materials to produce the end product (e.g., milk to produce yogurt) • End product minimally or not processed	• Biomass itself serves as an ingredient • Uses novel inexpensive feedstocks to produce high value proteins (e.g., agriculture remains) • Biomass minimally or not processed	• Host usually not present in the final product • Uses novel inexpensive feedstocks to produce high value ingredients (e.g., byproduct to produce proteins) • High purity – purification step
Product examples	*Yogurt, bread, cheese, tempeh, and alcoholic beverages*	*Mycoprotein (used as a base for whole-cut, alternative meat products)*	*Protein and Non-protein molecules (Flavoring agents, vitamins, pigments, fats, antioxidants)*

Genetic Modification






mRNA
Ribosome
Hydroxylation
Attaches a hydroxyl group (-OH) to a side chain of a protein
Phosphorylation
Adds a phosphate to serine, threonine or tyrosine
Methylation
Adds a methyl group, usually at lysine or arginine residues
Glycosylation
Attaches a sugar, usually to an "N" or "O" in an amino acid side chain
Lipidation
Attaches a lipid, such as a fatty acid, to a protein chain
Ubiquitination
Adds ubiquitin to lysine residue of a target protein for degradation
Protein
Acetylation
Adds an acetyl group to an N-terminus of a protein or at lysine residues
SUMOylation
Adds a small protein SUMO (small ubiquitin-like modifier) to a target protein
Disulfide Bond
Covalently links the "S" atoms of two different cysteine residues
R
OH
P
Me
Ub
Ac
Su
S—S


Concentration
• Protein Assay (Lowry, Kjeidhl)
• Quantitative Amino Acid Analysis
• UV-Vis Spectroscopy
• ELISA
Structure/Sequence
• N-and C-Termini
• Amino Acid Analysis
• Peptide Mapping and Sequencing
• Carbohydrate Analysis
• Mass Spectroscopy
• Disulfide Linkage
Size
• Electrophoresis
• Gel permeation Chromatography
• Field Flow Fractionation
• Ultrafiltration
• Light Scattering
Identity
• N-terminal Sequence
• Peptide Mapping
• Specific Bioassay
• Isoelectric Focussing
Protein Characterisation
Shape/Conformation
• Circular Dichroism
• X-Ray Diffraction
• FT Infrared
• NMR Spectroscopy
• Raman Spectroscopy
• Epitope Detection
• Specific Binding
Purity
• RP-HPLC
• Gel permeation Chromatography
• SDS-PAGE (Silver staining)
• Field Flow Fractionation
• Contaminant-specific ELISA
• Multiantigenic ELISA
• Immunoblot
• DNA-Assay
• LAL-Test
Surface Charge
• Isoelectric Focussing
• Chromato Focussing
• Ion Exchange Chromatography
Activity
• Bioassay *in-vivo*, *in-vitro*
• Specific Binding Assay

HOST	PROS	CONS
 **Bacteria**	• Prokaryotes – **easier to manage** • **Faster generation time** than other hosts • **Many available molecular tools** facilitating high yield • **Have plasmids**, the expression vectors integrated independently of host genome	• Genetic drift – **higher mutation rates** due to the fast generation time • **Bad public perception** (*E. coli*, the main model for engineering considered pathogen)
 **Yeast**  **Mold**	• Eukaryotes – **more robust than bacteria** (tolerate wider range of pH, temp, salts) • **High accumulation** levels of commercially available **compounds** (e.g., vitamins, organic acids) • Filamentous fungi **powerhouse enzyme producers**, extracellular enzymatic degradation	• **Slower generation time** • **Could require more nutrients**/substrates to grow than bacteria • Potential mold pathogenicity – **mycotoxins production** • **Negative impact** on product **rheology**
 **Microalgae**	• Eukaryotes – **more robust than bacteria** • **Adaptive in the same fermentation infrastructure used for bacteria or fungi** • **Heterotrophically grown** – more efficient, less expensive growth, **higher densities** • **Provide enormous** range of **unique molecules** (e.g., pigments, fatty acids)	• **Target extraction challenging**, presence of tough cell walls (silica-based coatings) • **Autotrophically grown** – slow growth, **low density**

Pre-Clinical & Post-Production Testing Requirements

Each strain requires comprehensive identification, safety and pre-clinical efficacy testing.

SAFETY & CHARACTERIZATION

- Full genome sequencing & analysis
- Deleterious gene analysis
- Plasmid analysis
- Fermentation media optimization (allergen free)
- Acid survivability
- Bile sale survivability
- Hemolytic activity
- Whole Genome Sequence (DNA composition)
- Annotated genome analysis
- gyrB Gene sequence analysis
- Phylogenetic Placement
- Genome Allergen Analysis
- Genome outer membrane analysis
- Cytotoxicity testing
- Virulence testing
- PCR toxin screen
- Zones of hemolysis testing
- Anti-microbial susceptibility
- Zone of inhibition/Antibiotic susceptibility

IDENTIFICATION

- Gram stain
- Primer design
- ID Method (PCR, etc)
- Enumeration Validation

EFFICACY

- Substrate analysis
- Nutrient analysis
- Enzyme Production
- Bio-Actives Production
- Cell-signaling molecules
- Antioxidants
- Antimicrobials
- pH profile
- Temperature profile
- CaCo2 cell adhesion
- Hormones
- Ex-vivo efficacy testing

Post-production, each strain undergoes testing an optimization to ensure it's fit for purpose in a variety of dietary supplement and functional food/beverage applications.

POST-PRODUCTION

- Stability testing
- Matrix Interference Analysis
- Freeze Dryer Trials
- Product/Yield Optimization

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 2: New Methodologies to Produce Existing Dietary Ingredients

March 27, 2026

Anthony Pavel

Partner

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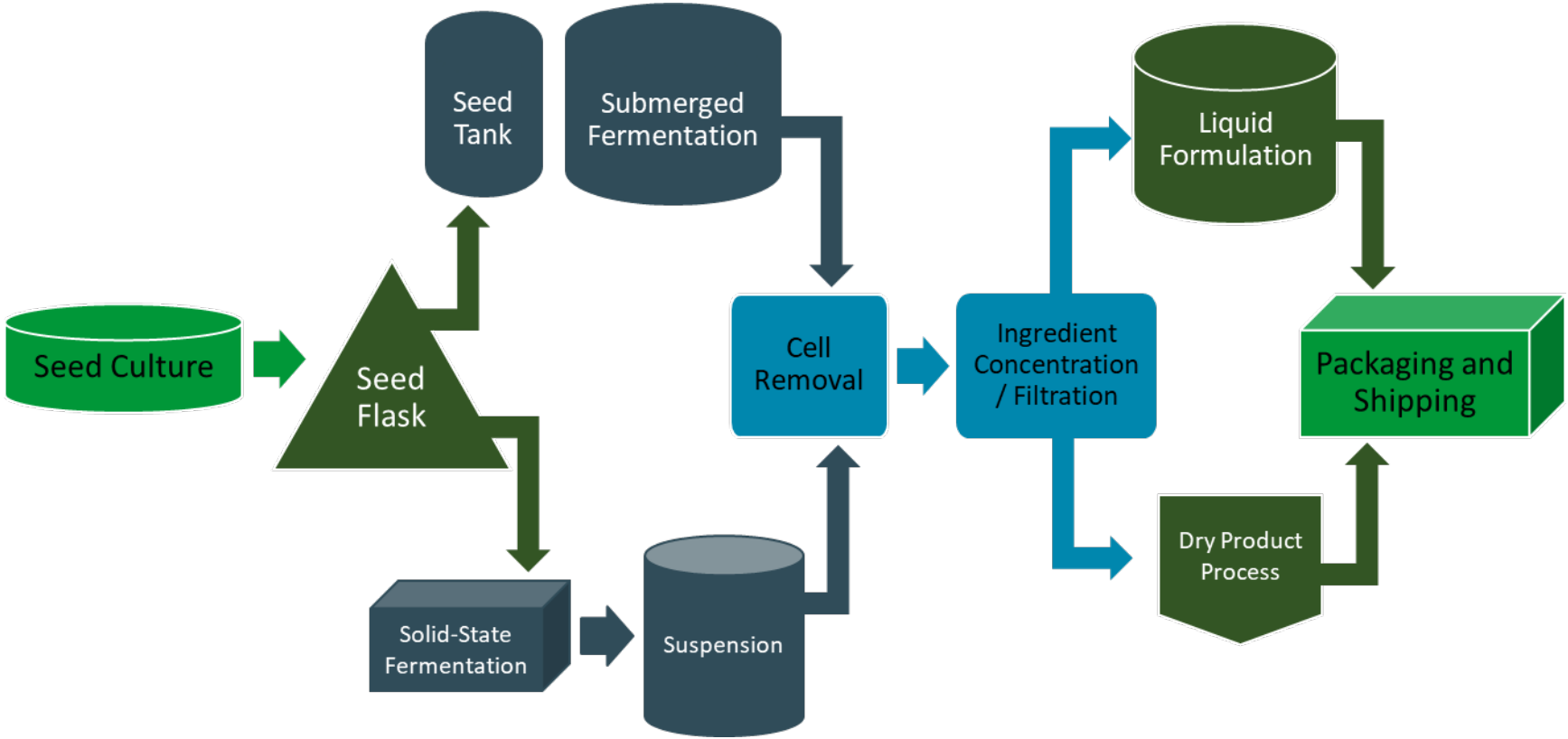
Regulatory Safety Evaluation Framework

- There are existing, robust frameworks for the regulatory and safety evaluation of dietary ingredients produced with new methodologies
- Ingredients produced using Microbial Fermentation (Precision Fermentation) provides a well tested and utilized model
- “New” is a relative term – modern techniques using microbial fermentation date back to the 1970s, and molecular engineering methods have been evolving for the last ~35 years
  - Vitamins, enzymes, steviol glycosides, beta-lactoglobulin, lactoferrin, peptides …
- Regulatory and safety evaluation framework is well established

General Manufacturing Process - PF



Safety Evaluation Framework - Key Elements

- **Product Identity and specifications**
  - substance, chemical name, CAS No., chemical formula and structure; chemical composition, physical properties, heavy metals and micro specs.; 3-5 batch analyses
- **Method of manufacture**
  - flow chart, step-by-step description, raw materials, processing aids, microorganism, strain genetic modifications
- **Intended uses and dietary exposure (EDI)**
  - exposure of substance from proposed uses
- **Safety data (NOAEL, ADI)**
  - acute, subacute, subchronic, chronic, genotoxicity, carcinogenicity, allergenicity
- **Allergenicity**
  - literature, *in silico* methods (*i.e.*, FARRP's Allergen Online), *in vitro* digestibility studies
- **Safety assessment**

Safety Evaluation Framework

- Identity of the substance / dietary ingredient
  - Detailed characterization of the ingredient - Systematic numbers; IUPAC; ATCC; Synonyms; Appearance; Molecular mass; Molecular formula; Amino Acid Sequence; Structure; Composition of substance (typical analyses such as water, protein, ash, total organic solids, activity, etc.)

- Production Organism
  - Non-toxigenic / Non-pathogenic; documentation of Safe Strain Lineage – use in food / food production, repeated tox studies, Pariza Johnson Decision tree*
  - Modifications – non-toxigenic, poorly mobilizable, well characterized sequence, using common and well understood techniques

*Pariza MW, Johnson EA. Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century. Regul Toxicol Pharmacol. 2001 Apr;33(2):173-86. doi: 10.1006/rtph.2001.1466. PMID: 11350200.

Safety Evaluation Framework

- Manufacturing Process
  - cGMP / Quality Systems
  - Inputs / raw materials are food grade
  - Aseptic procedures and monitoring / critical control points for contamination
  - Downstream processing / filtration
  - Demonstration of manufacturing control through analysis of non-consecutive lots
  - Where appropriate - verification via finished product testing

Safety Evaluation Framework

- Safety Studies / Data
  - Published pivotal safety data where available
  - Toxicity data – using batches representative of commercial production
  - FDA Redbook
    - Example matrix:
      - Genotox – Ames test, chromosomal aberration
      - Allergenicity and toxin screening - *in silico* allergenic sequence homology
      - Oral tox studies when warranted
      - Other data as warranted

Safety Evaluation Framework

- Exposure Evaluation & Safety Margin
  - Exposure / Estimated Daily Intake (EDI)
    - Daily consumption per person per kg/bw
    - Evaluation of other sources of intake (NHANES)
    - Change at the high user – eg 90th percentile
  - Safety Margin
    - NOAEL: No-Observed-Adverse-Effect-Level
    - ADI: Acceptable Daily Intake = $NOAEL/SF$
    - SF: Safety Factor = 100 – 1000
    - MOS: Margin of Safety = $ADI/EDI \geq 1$
    - Conservative assumptions should be used

References and Resources

A selection – not a complete list!

- FDA - Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives, June 2014
- Pariza MW, Johnson EA. Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century. Regul Toxicol Pharmacol. 2001 Apr;33(2):173-86. doi: 10.1006/rtph.2001.1466. PMID: 11350200.
- Pariza MW, Gillies KO, Kraak-Ripple SF, Leyer G, Smith AB. Determining the safety of microbial cultures for consumption by humans and animals. Regul Toxicol Pharmacol. 2015 Oct;73(1):164-71. doi: 10.1016/j.yrtph.2015.07.003. Epub 2015 Jul 9. PMID: 26165564.
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- Crincoli CM, van de Ligt JLG, Eapen AK, Pavel AT, Hanlon PR, Almond-Abbate K, Haugabrooks E, Hlywka J, Lu V, de Mooij F, Pandis M, Peterson R, Petrick JS, Ranganathan P, Henderson RG. A tool to support food substance safety evaluations in the United States. Regul Toxicol Pharmacol. 2025 Sep;161:105838. doi: 10.1016/j.yrtph.2025.105838. Epub 2025 May 3. PMID: 40324559.
- Guidance for Industry and Other Stakeholders: Redbook 2000, Toxicological Principles for the Safety Assessment of Food Ingredients, July 2007
- FDA - Statement of Policy - Foods Derived from New Plant Varieties, May 1992
- Precision Fermentation Alliance https://www.pfalliance.org/

Thank You

Any questions?

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Enabling a Healthier World

Capsugel® | Lonza

Innovation at the interface of ingredient science and dosage form design

Session 2: New methodologies to produce existing dietary ingredients

March 27, 2026

Meet our speaker

Capsugel® | Lonza

Frank Romanski, Ph.D.

Vice President, Strategic Growth & Revenue Management Lonza Capsugel

Ph.D. in Chemical Engineering from
Rutgers University

Background in R&D, business management, marketing, and strategy

Leads global growth and revenue management across:

Hard Empty Capsules (HEC)

Dosage Forms Solutions (DFS)

Ingredients

Global Pharmaceutical Solutions (GPS)

Brings a dual perspective across pharma + nutra regulated markets, working as both an **ingredient supplier** and **dosage form manufacturer** globally

Integrated insights across the value chain

Capsugel® | Lonza

Development — Commercial

		Development Services	Health Ingredients	Capsule Production	Tablet Production	Capsule filling services and equipment	Packaging services	Logistic services
Nutra	**Solid fill** (HEC)		✓	✓		✓		
	Liquid fill (DFS)	✓	✓	✓		✓	✓	
Pharma	**Solid fill** (HEC)	✓		✓		✓		
	Liquid fill (GPS)	✓		✓		✓		
	Specialty	✓		✓	✓	✓	✓	✓

Note: Hard Empty Capsule (HEC), Dosage Form Solutions (DFS), and Global Pharmaceutical Solutions (GPS)

What we are observing across the industry

Capsugel® | Lonza

How production method and supplier differences translate into formulation challenges

Industry realities when bringing new ingredients to market

Ingredient variability

Synthetic, fermentation, and extraction routes produce ingredients with differing matricies, impurities, and stability profiles

Analytical and supplier differences

Different analytical methods and processes lead to COA variability across suppliers

Formulation and performance impact

Upstream variability affects stability, reactivity, and compatibility

- Even “simple” ingredients behave differently depending on production route. Complex ingredients like botanicals and probiotics further increase variability
- Ingredient variability can alter release behavior, limit encapsulation compatibility, and create distinct impurity profiles across production routes (e.g. synthetic vs. fermentation L-Carnitine)

Advanced delivery systems such as **capsule-in-capsule DUOCAP® capsules** or **Enprotect® bi-layered capsules for enteric delivery** are often used to help mitigate stability, compatibility or delivery challenges

Capsugel® | Lonza

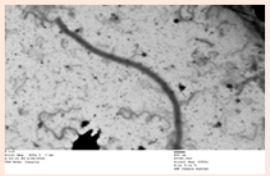
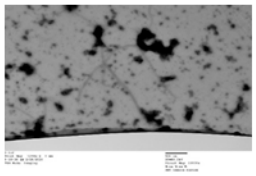
Ingredient case studies

In action

Ingredient case study – UC-II®

Capsugel® | Lonza

Preserving native structure and understanding analytical differences

	UC-II®	Other native type II collagen
Microscopic observations		
Structure	Intact collagen fibers (unhydrolyzed)	Partially hydrolyzed
Method of analysis	**ELISA** (Specific for undenatured type II collagen epitopes)	**HPLC** (no specificity, only measures total collagen based on Hydroxyproline content)

Note: Enzyme-Linked Immunosorbent Assay (ELISA), High Performance Liquid Chromatography (HPLC)

UC-II® is undenatured type II collagen is preserved through **low temperature processing**, allowing the presence of undenatured epitopes

ELISA (epitope based)	**HPLC / Hydroxyproline** (total collagen)
Detects epitopes associated with undenatured type II collagen	Measures total collagen only
Structure-specific	Not structure specific
Can confirm presence of undenatured collagen	Cannot differentiate undenatured vs. hydrolyzed collagen

Ingredient case study – DUOCAP®

Capsugel® | Lonza

Performance of health ingredients significantly impacted by delivery formulation

SHIME® in vitro model assesses intestinal release of acid sensitive digestive enzymes

Study objective:

In vitro evaluation of different capsule polymer combinations for targeted delivery of an acid-sensitive digestive enzyme (Pancreatin) in upper
GI model

Test methodology:

SHIME®* in vitro GI model:
stomach → duodenum → jejunum

Capsules tested: Vcaps® Plus, DRcaps®, DUOCAP®*

Actives: caffeine (release marker), pancreatin (acid-sensitive enzyme)

Conditions: fasted + fed

Measures: enzyme activity was assessed via tributyrin to butyrate conversion

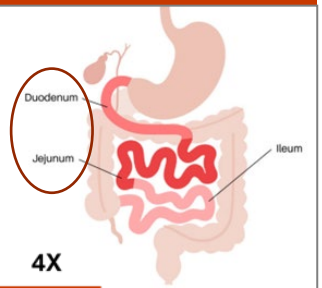
DUOCAP® capsule polymer combinations evaluated:

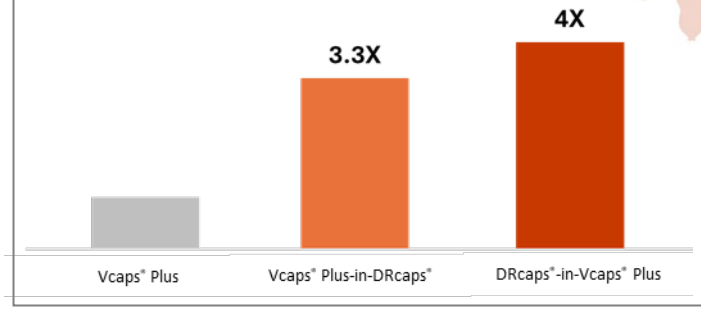
Outer capsule	Inner capsule	Group acronym
DRcaps®	Vcaps® Plus	**VCP-in-DR**
Vcaps® Plus	DRcaps®	**DR-in-VCP**
Vcaps® Plus	---	**Single VCP**

Multi-fold increase in enzyme activity compared to immediate release capsules in upper small intestine when taken with food

Enzyme activity:

DUOCAP® capsule-in-capsule technology delivers **up to**
4x more enzyme activity compared to immediate release capsules





Source: Evaluation of Targeted-Release Capsule Formulations for Protection of the Acid-Sensitive Enzyme Pancreatin Under Fasted and Fed Intestinal Conditions In Vitro

Note: DR-in-DR data not shown; as this format is best suited for colon delivery.
*Simulator of the Human Intestinal Microbial Ecosystem (SHIME®)

In conclusion

Considerations and opinions

Closing considerations and opening for future collaborations

Capsugel® | Lonza

Regulatory clarity on novel production methods

Tiered comparability: greater data requirements only when a new production method materially changes key product attributes

Define **trigger for "meaningful change"** by ingredient class

Clarify how to **assess hybrid or multi-modality ingredients** outside standard categories

Analytical method expectations

Guidance on **aligning method specificity** with ingredient complexity and production route

Set **expectations for characterizing** process-related impurities, residuals and by-products

Define what counts as **adequate comparability evidence** across suppliers, production methods, and batches

Regulatory framework gaps

Reduce uncertainty by **unifying federal/state guidance** under DSHEA

Explain how GRAS and dietary supplement pathways align for **tech-enabled ingredients**

Clarify **drug preclusion** for novel bioactives and tech-enabled ingredients

Collaboration path forward

Establish compliant pathways for **novel ingredient development** and market entry

Strengthen **FDA-industry dialogue** across the value chain

Encourage **practical pre-submission engagement** on novel methodologies

Enable clearer pathways for **compliant market entry**

Thank you

Session 2 Reminders

There is some overlap in today's topics.

- Please keep your Q&A in-line with this session – scientific and technical advancements in dietary ingredient production (e.g., synthesis, precision fermentation, cell culture technology, and recombinant production) and the impact on the attributes of these produced dietary ingredients

During Q&A:

- Be sure to speak your remarks into the microphones.
- Introduce yourself with your name and organization

April 27th is the deadline for submission of comments to the docket (No. FDA-2026-N-2047).

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 2:
Question and Answer

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Reminder: If you leave for lunch, you will need to be rescreened upon re-entry to the building. Please plan accordingly and arrive with enough time to traverse security.

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Currently on break

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 3:
Identity attributes for ingredient types

Moderator: Betsy Jean Yakes, Identity and Status Branch Chief, DRE, ODSP, HFP, FDA

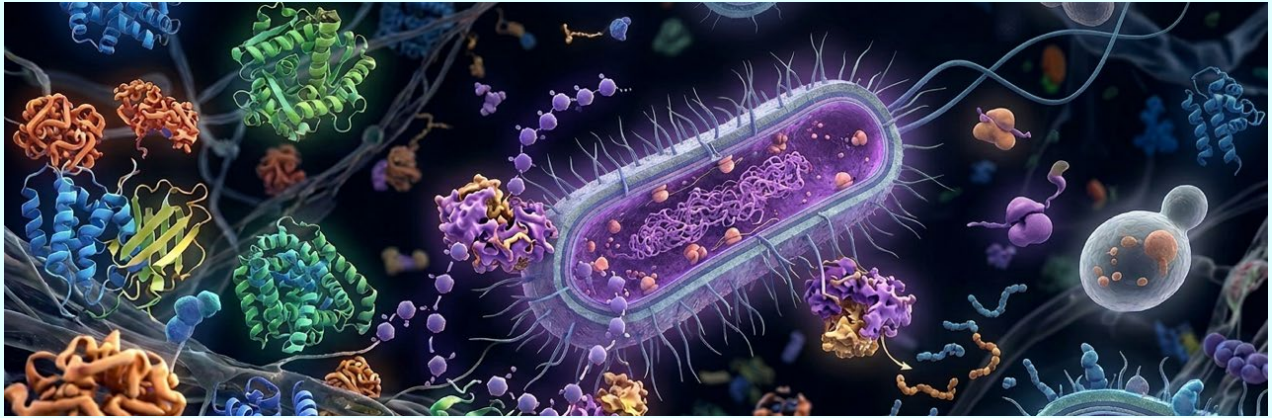
Panelists:
3.1 Elvira Gonzalez de Mejia, Professor, University of Illinois Urbana-Champaign
3.2 Linda Neckmar, Senior Vice President Human Health, Novonesis
3.3 Andrea Wong, Senior Vice President & Chief Science Officer, Council for Responsible Nutrition
3.4 Gregory Leyer, Founder, Biotic Solutions Consulting
3.5 Amy Smith, Sr. Director, Medical Affairs North America, Kerry ProActive Health

Session 3: Identity attributes for ingredient types such as proteins, enzymes, and microbials

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Betsy Jean Yakes, PhD
FDA/HFP/OFCSDSI/ODSP/DRE/Identity and Status Branch Chief

Friday, March 27, 2026
College Park, MD

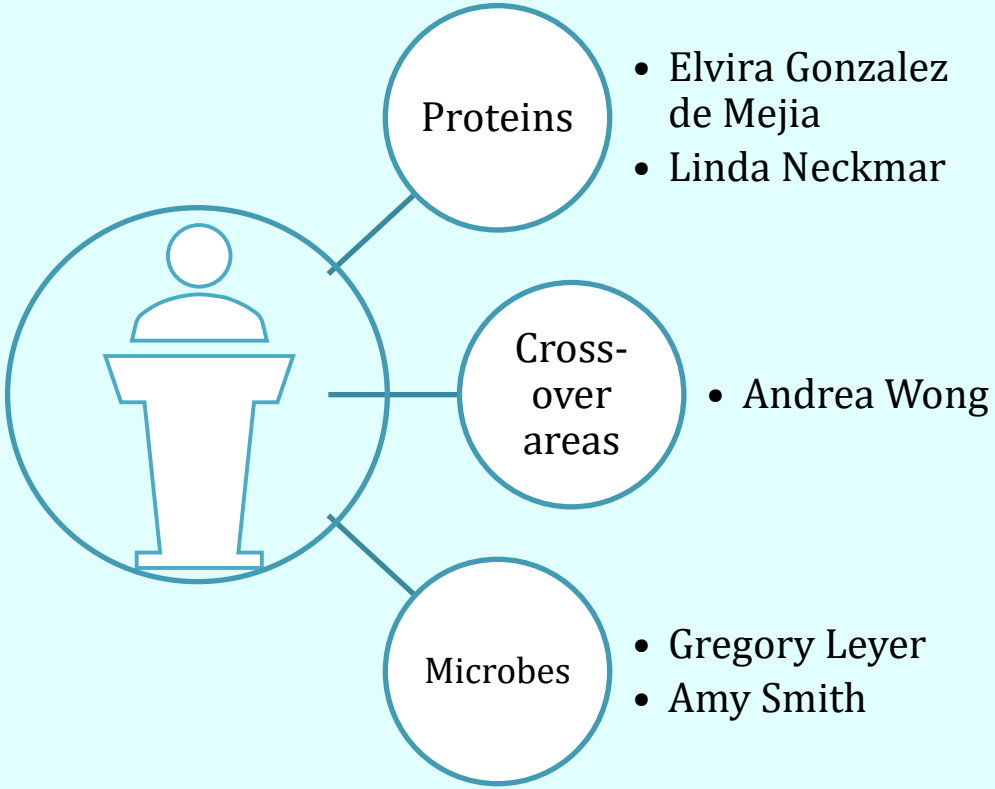


Overview

Explore questions related to:

- determining the **identity** of proteins, enzymes, and microorganisms, which are not specifically listed in 201(ff)(1)
- evaluating **attributes** that are important for assessing identity.

Speakers 1:00-2:00 and Q&A 2:00-2:15



Proteins, Enzymes, and Microbials

INGREDIENT CATEGORY

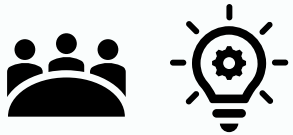
- Commonly under 201(ff)(1)(E) "a dietary substance for use by man…"

INTERPRETATION

- A substance that is commonly used as human food or drink

RENEWED DISCUSSION

- How do non-food articles fit?
- What are the key identity attributes?



What identity attributes are important in determining whether something is a “dietary ingredient”?

What level of modification of a dietary substance creates a new ingredient?

amino acid sequence, molecular weight distribution, post-translational modifications, enzyme activity, bioactivity markers

Structure/function; synthetic production; amino acid substitutions, insertions, deletions; post-translation modifications

sequence, strain ID, viability, metabolic profile, virulence factors, antibiotic resistance

strain-level differences (e.g., genetic or phenotypic); functional changes; food constituent vs. incidental component vs. contaminant

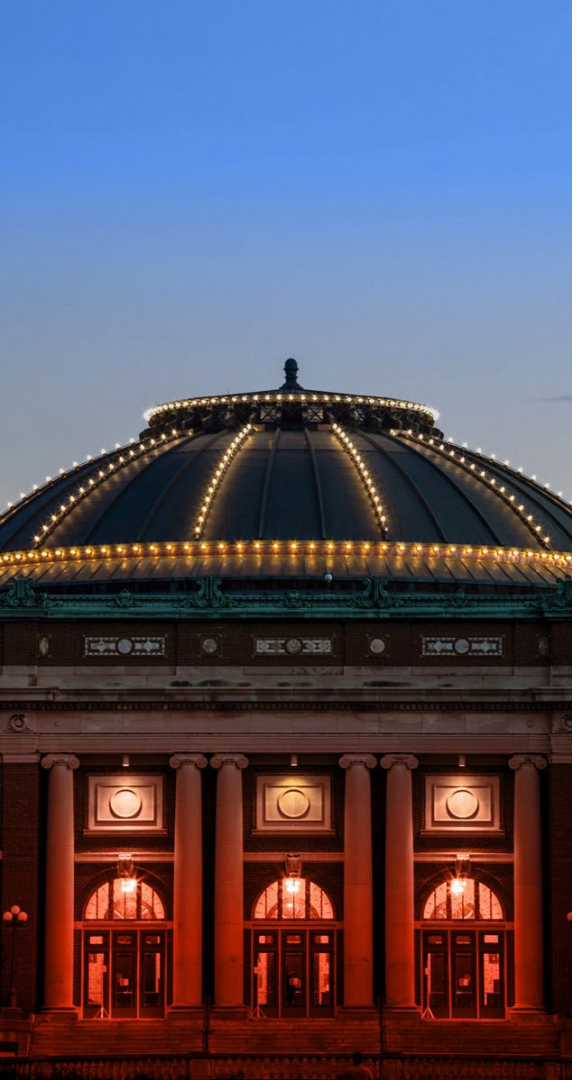

FDA
U.S. FOOD & DRUG
ADMINISTRATION

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Human Foods Program U.S. Food and Drug Administration

Elvira Gonzalez de Mejia, Ph. D.
Professor, University of Illinois Urbana-Champaign
Friday, March 27, 2026

ILLINOIS



Session 3: Identity attributes for ingredient types such as proteins, peptides and enzymes

- Definitions and sources
- Technological approaches and their impact on quality attributes of proteins, peptides and enzymes
- Potential changes on quality attributes that may affect safety
- Determine the most important quality attributes to establish their identity

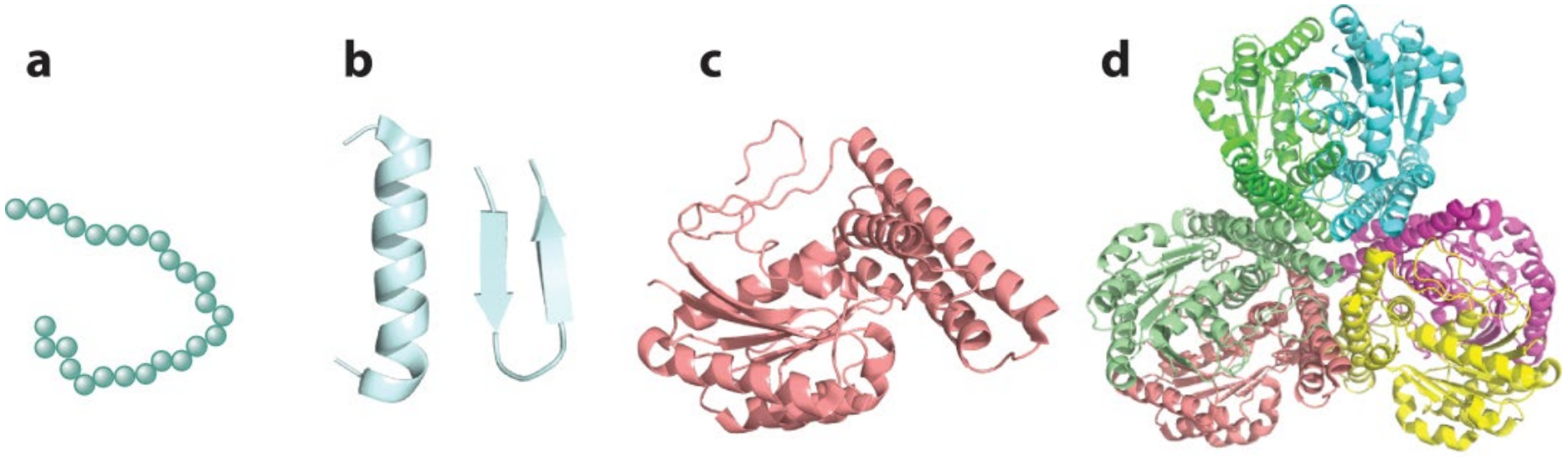
Definitions

- Proteins are typically presented as nutritional or structural ingredients.
- A peptide is a smaller fraction of a protein, with different identity and properties, potentially possessing specific biological activities.
- An enzyme is a protein whose central characteristic is its measurable functional activity.

https://www.wwpdb.org/

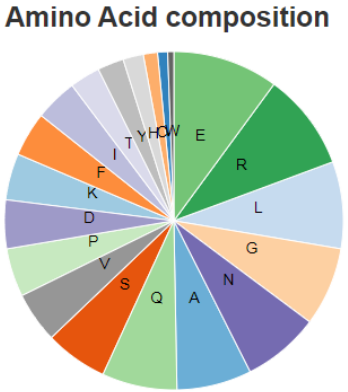
High molecular weight biopolymers made by linking L-α-amino acids through a peptide bond.

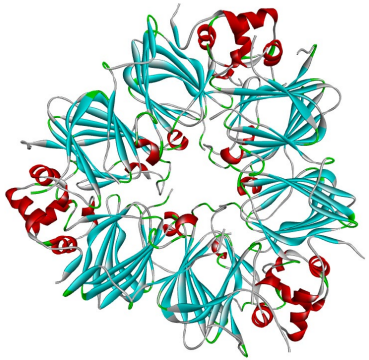
Nature Structural Biology **10**, 980 (2003) **doi: 10.1038/nsb1203-980**



Helmick H, et al. 2023
Annu. Rev. Food Sci. Technol. 14:203–24

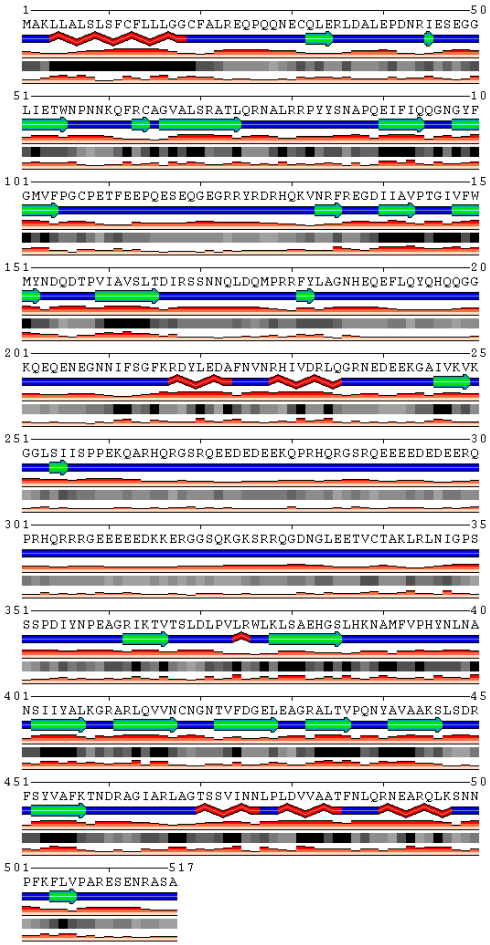
Legumin A





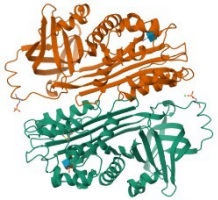
Predicted secondary structure using Minnou tool, http://minnou.cchmc.org/

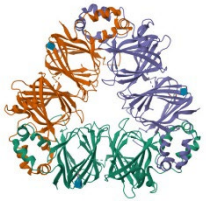
Protein	Source	Percent identity
Legumin A2	Vicia faba (Faba bean)	86.9
Legumin A	Cicer arietinum (Chickpea)	79.9
Glycinin	Glycine max (Soybean)	42.2
Legumin	Phaseolus vulgaris (Common bean)	38.3

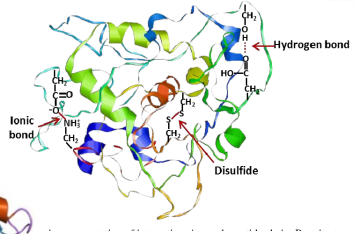


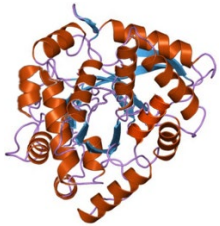
Classification of Proteins Based on Solubility

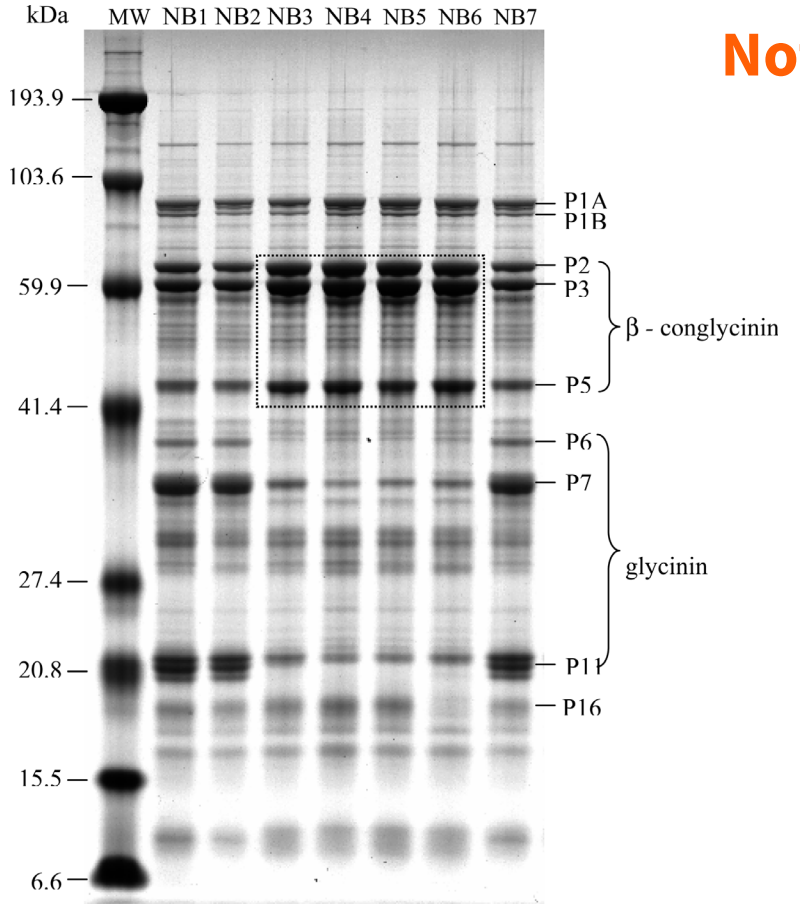
- **Albumins** – (e.g., serum albumin, **ovalbumin**, and α-lactalbumin)
  - Soluble in water (pH~6.6)
- **Globulins** – (e.g., glycinin, **phaseolin**, and β-lactoglobulin)
  - Soluble in diluted salt solutions (pH 7.0)
- **Glutelins** – (e.g., wheat **glutelins**)
  - Soluble in acid (pH = 2) and alkali (pH = 12)
- **Prolamins** – (e.g., zein and **gliadins**)
  - Soluble in 70% alcohol











Not all Dietary Proteins are Created Equal

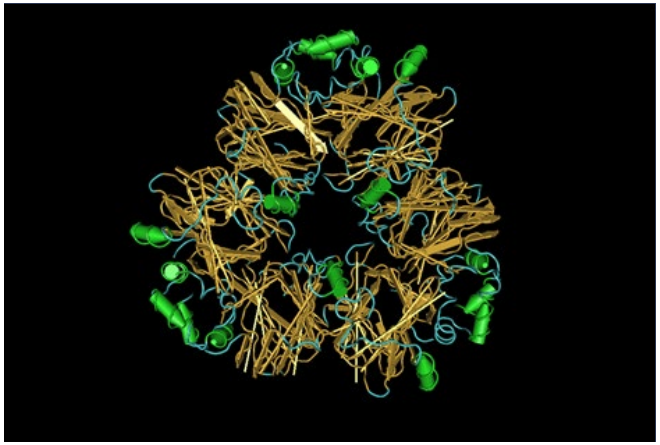
Protein profiles of soy flours from seven soy genotypes (NB1-NB7).

Major protein bands:

- P1A, lipoxygenases 2 and 3;
- P1B, lipoxygenase1;
- P2, α′ subunit of β-conglycinin;
- P3, α subunit of β-conglycinin;
- P5, β subunit of β-conglycinin;
- P6, glycinin A3 chain;
- P7, glycinin A1,2,4 chains;
- P11, glycinin basic chains;
- P16, Kunitz trypsin inhibitor

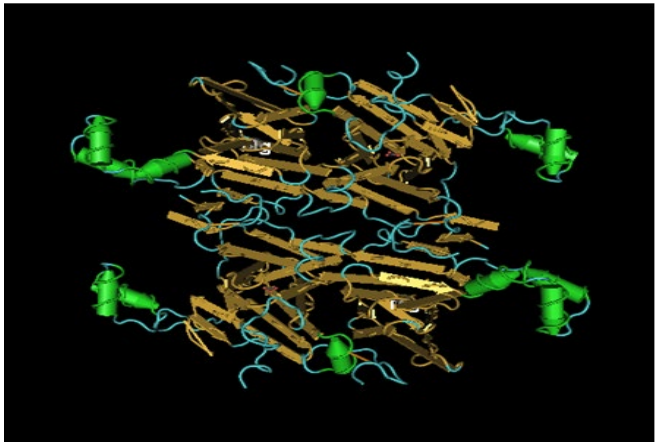
Wang, Rupasinghe, Schuler, Gonzalez **de Mejia**. 2008. Identification and characterization of topoisomerase II inhibitory peptides from soy protein hydrolysates. J. Agric. Food Chem. 56 (15): 6267-6277.

Crystal Structure of Proteins



Glycinin A3B4 **subunit** homo hexamer

Printed with permission. Adachi et al., 2003. Proc. Nat. Acad. Sci.USA 10: 7395.



β-Conglycinin α'-homotrimer

Printed with permission. Maruyama et al., 2004. Acta Crystallogr., Sect.D 60 pp. 289. 1B.

Examples of Regular Protein Structure: Triple Helix

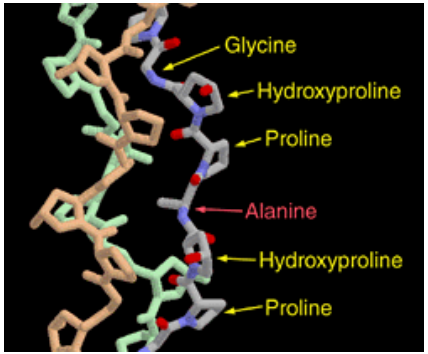
Collagen – structural protein

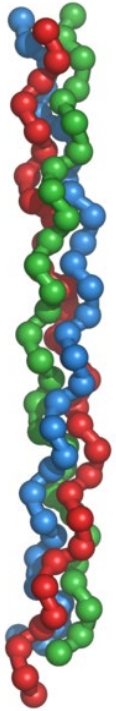
- Rigid and inextensible
- Major constituent of tendons & connective tissues
- Characterized by repetitious tripeptide sequence

Glycine-X-proline or glycine-X-hydroxyproline

X = any amino acid

Hydroxyproline: hydroxylated derivative of proline





Importance of Proteins

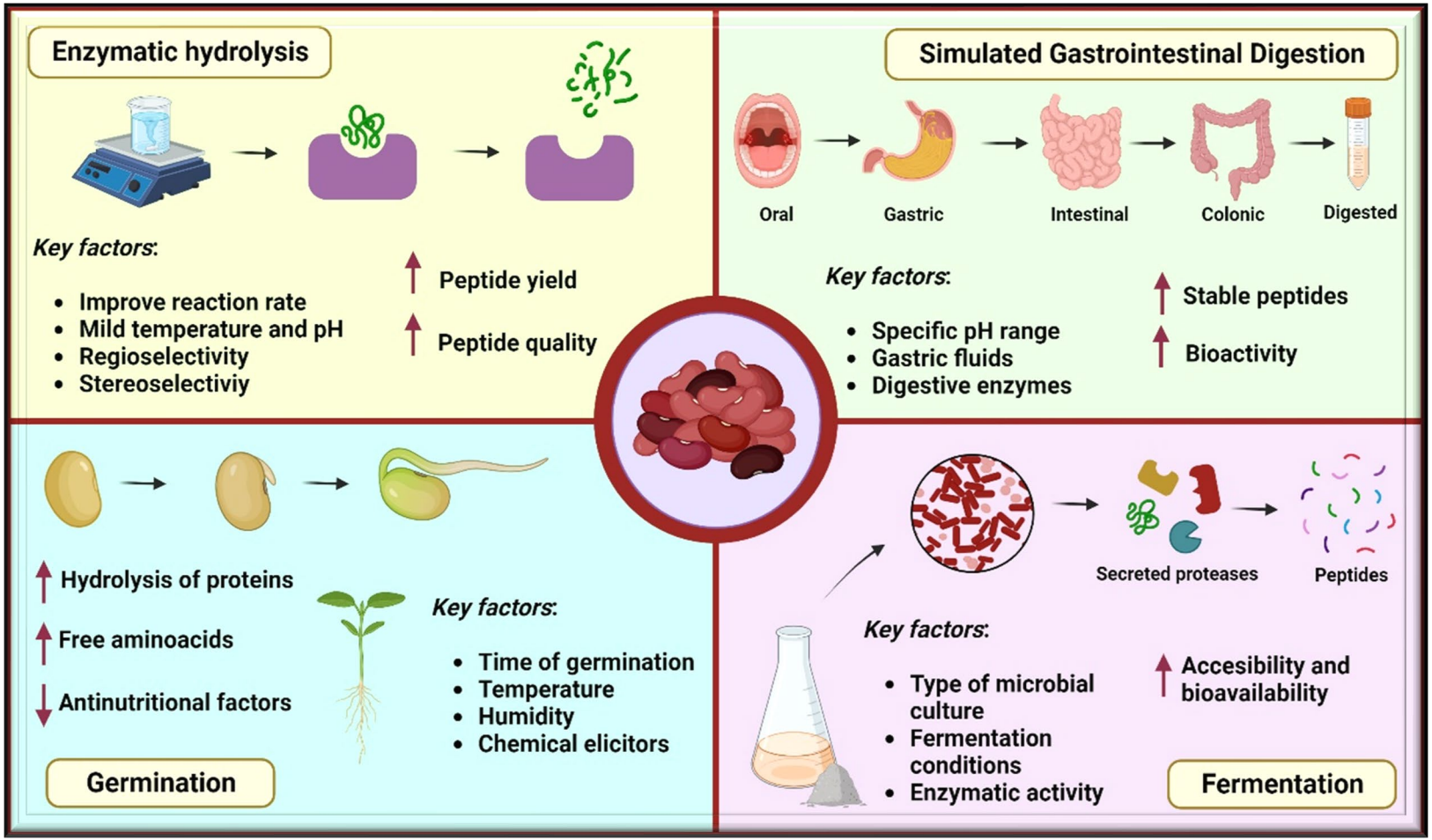
Proteins play **crucial roles in fundamental life** processes and are present in the form of:

- **Enzymes**
- **Structural proteins** (collagen, elastin, keratin)
- **Contractile proteins** (myosin, actin, tubulin)
- **Carrier proteins** (hemoglobin, myoglobin, transferring, ceruloplasmin, plasma lipoproteins, plasma albumin)
- **Hormones** (insulin, growth hormones)
- **Storage proteins** (ferritin, casein, ovalbumin, lipovitellin, gliadins, glutenins, zeins)
- **Receptors** (rhodopsin)

In the **food industry** as food ingredients:

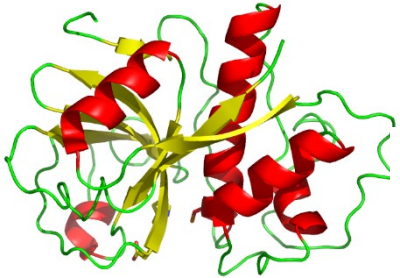
- **Water binding**
- **Viscosity** (thickening of soups, sauces)
- **Cohesiveness and elasticity**
- **Emulsifying agents** (meat sausage)
- **Flavor, colors** (myoglobin, Maillard browning)
- **Foams** (whipping dessert toppings)
- **Provide body**
- **Buffers**
- **Nutritive value**
- **Enzymes**
- **Fat adsorption** (reduction of free fat in cooked meat products)

Methods of Peptide Production are Diverse



Fonseca Hernández, Mojica, Gonzalez de Mejia. 2024. Current Opinion in Food Science 56, 101132 .

Food Enzymes

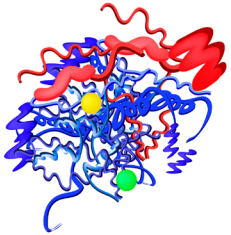


Papain

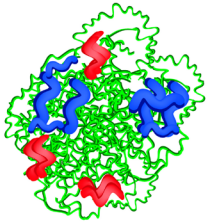
Ficin

Bromelain

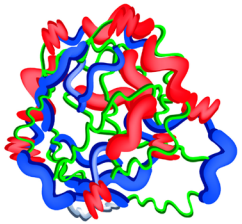
Digestion Enzymes



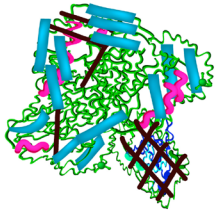
Amylase



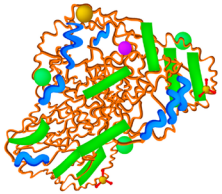
Trypsin



Pepsin



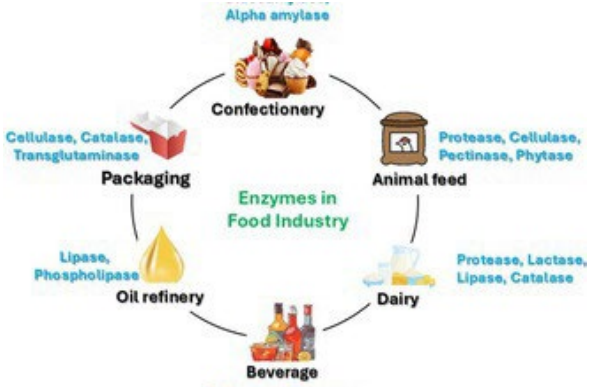
Lipase

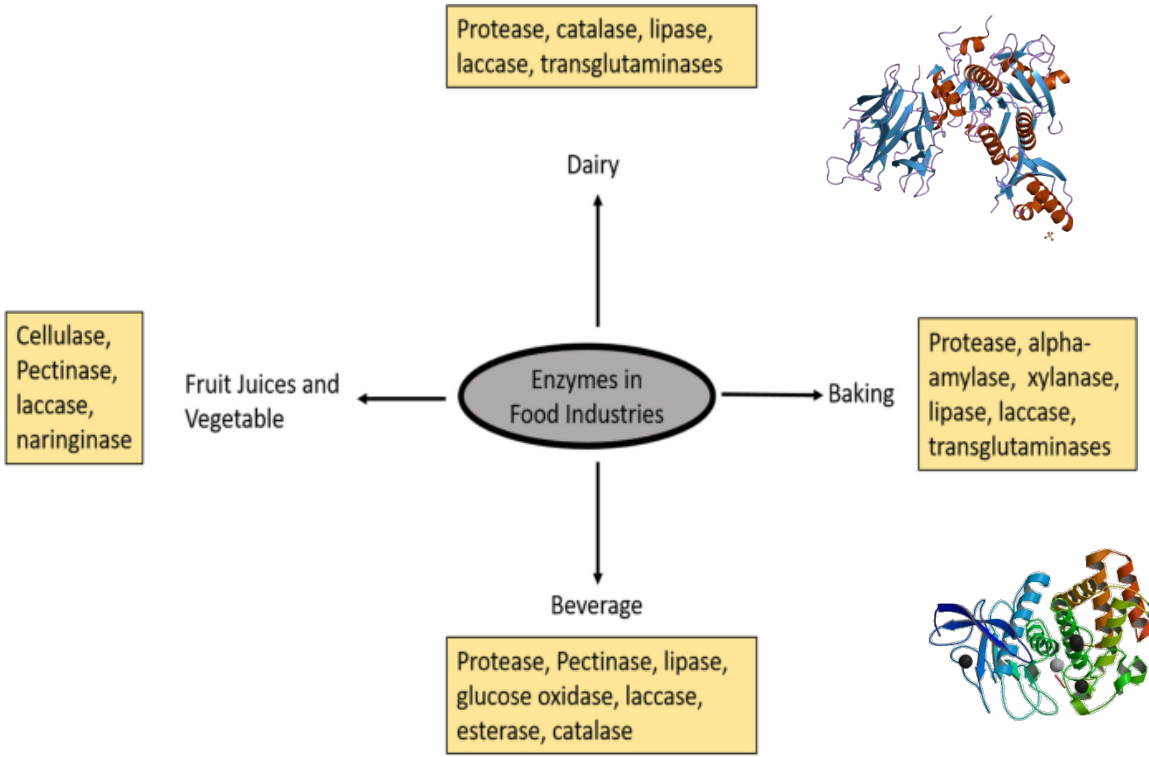


Gelatinase

Aider M. Potential applications of ficin in the production of traditional cheeses and protein Hydrolysates. JDS Communications, 2021; 2, 233-237

Food Enzymes





Kumar *et al*. Microbial enzymes and major applications in the food industry: a concise review. Food Prod Process and Nutr **6**, 85 (2024). https://doi.org/10.1186/s43014-024-00261-5

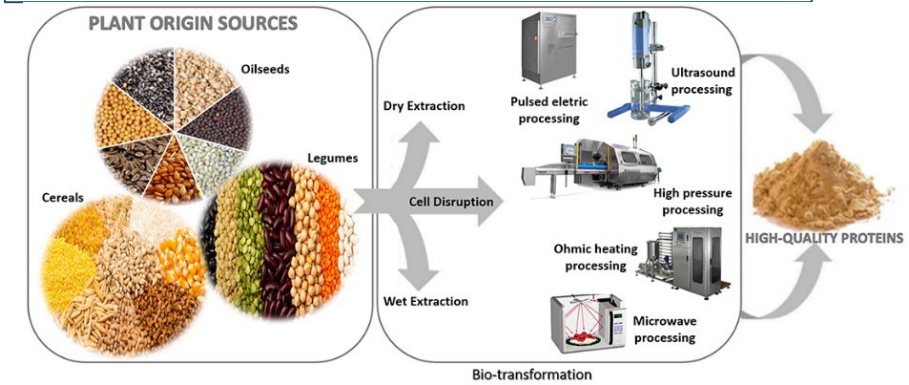
Siddikey et al.. Enzyme Technology in the Food Industry: Molecular Mechanisms, Applications, and Sustainable Innovations. Food Sci Nutr. 2025;13(9):e70927. doi: 10.1002/fsn3.70927.

Types of Products

Protein Supplements

Protein Hydrolisates and Bioactive Peptides

Protein hydrolysates can be produced from several sources using methods aimed to disrupt protein structures and produce bioactive peptides



Cruz-Solís *et al*. (2023). Alkaline extraction-isoelectric precipitation of plant proteins. In: Hernández-Álvares, A. et al., *Green processing technologies from plants* (First, 1-19). *Springer.*

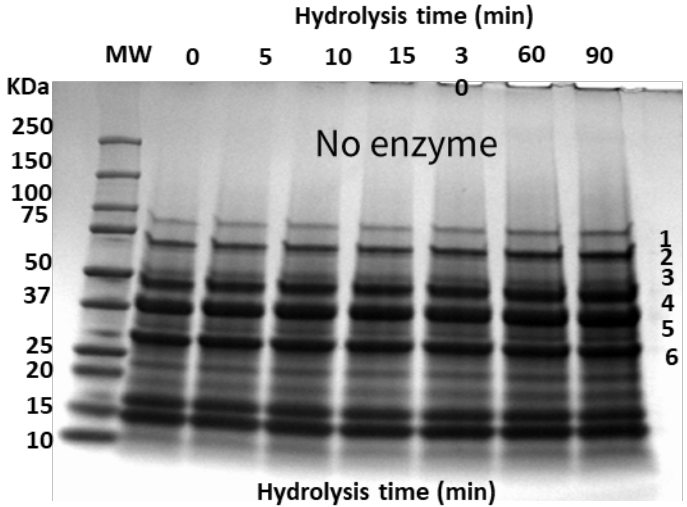
Gomes-Almeida *et al.* (2020). Plant proteins as high-quality nutritional source for human diet. *Trends in Food Science and Technology,* 97, 170-184.

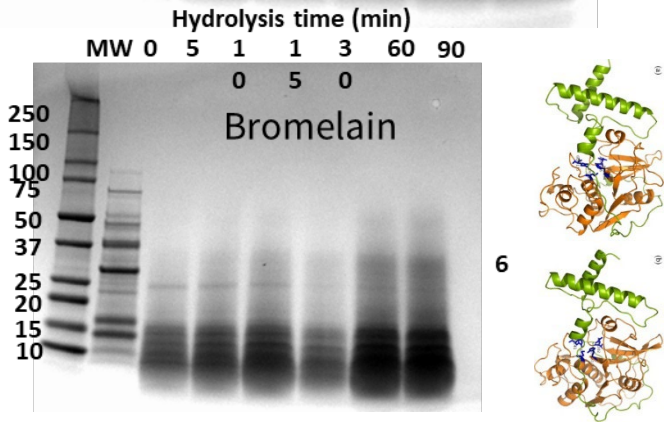
Kumar *et al*. (2022). Plant-based proteins and their multifaceted industrial applications. *LWT, 154,* 112620.

Protein Hydrolysates and Peptides

Protein hydrolysates are produced from the extensive or partial hydrolysis of protein-peptide bonds, yielding a complex mixture of **peptides, oligopeptides, and free amino acids**

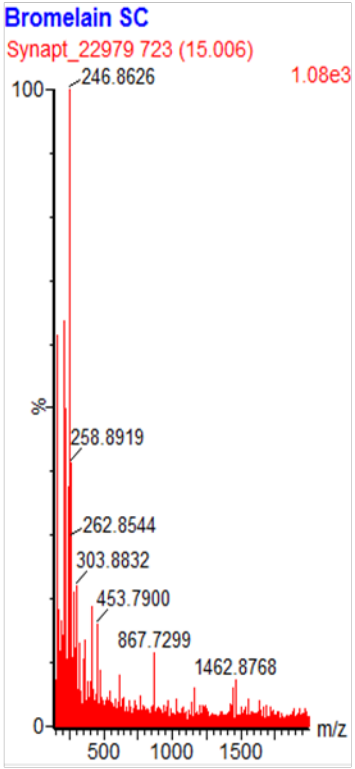
Bioactive peptides are small peptides (2-20 amino acids, 3-6 kDa or less) with several physicochemical and biological functions



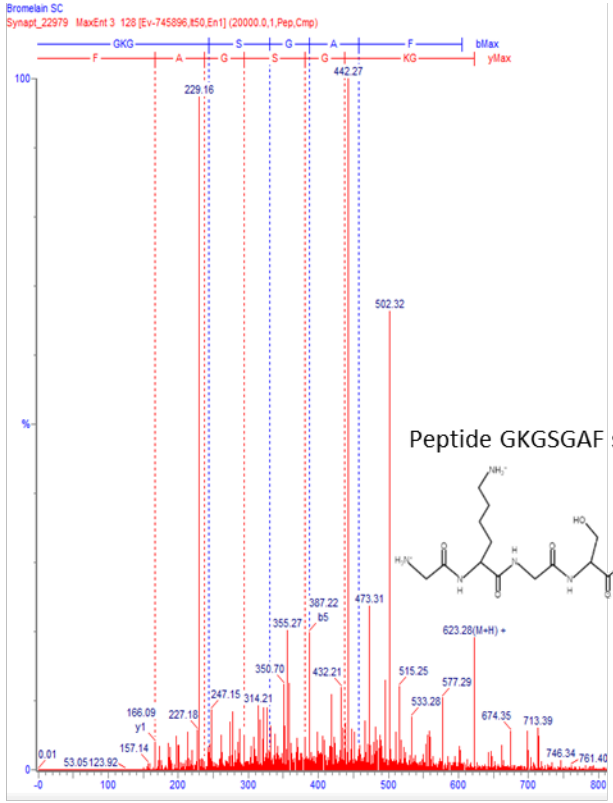


Cruz-Solís *et al*. (2023). Alkaline extraction-isoelectric precipitation of plant proteins. In: Hernández-Álvarez, A. et al., *Green processing technologies from plants* (First, 1-19). *Springer*.
Sá *et al.* (2020). Plant proteins as high-quality nutritional source for human diet. *Trends in Food Science and Technology*, 97, 170-184.
Kumar *et al*. (2022). Plant-based proteins and their multifaceted industrial applications. *LWT, 154,* 112620.
Yamazaki *et al*. (2019). Effective food ingredients for fatty liver: soy protein β-conglycinin and fish oil. *International Journal of Molecular Sciences, 19*(12), 4107

Methods to Determine Identity



Peptide GKGSGAF fragmentation pattern



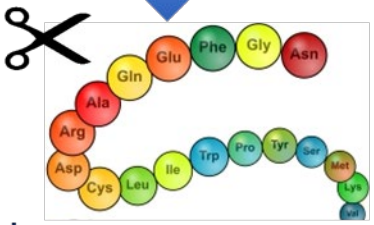
Peptide GKGSGAF sequencing

- ✓ Degree of hydrolysis
- ✓ Physicochemical parameters (MW, pI, hydrophilicity, charge)
- ✓ Soluble protein
- ✓ SDS-PAGE electrophoresis
- ✓ Peptides sequences (protein structure prediction)
- ✓ Liquid chromatography (molecule weight, purity)
- ✓ HPLC separation, further concentration
- ✓ Mass spectrometry (triple stage Model API-III, ESI-MS/MS, MALDITOF-MS (sequence, quantity)
- ✓ Databases search for activities

Optimization of the Production of Peptides

Black beans

Black bean hydrolyzed protein isolate (HPI)



Protease

1= Trypsin
2= Flavourzyme
3= Proteinase k
4= Thermolysin
5= Alcalase
6= Pepsin EC
7=Papain
8= Chymotrypsin

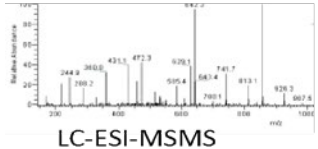
E/S ratio

R1 = 1:20
R2 = 1:30
R3 = 1:50

Time of hydrolysis

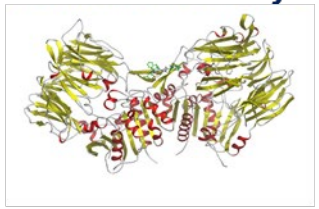
T1 = 120 min
T2 = 180 min
T3 = 240 min

Characterization

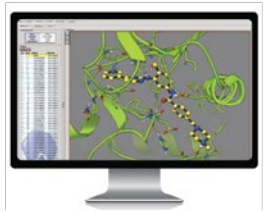


LC-ESI-MSMS
MALDI-TOF

Biochemical assays

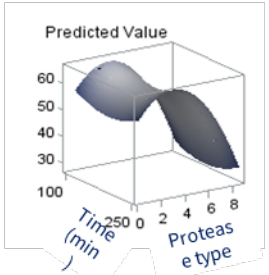


In silico docking

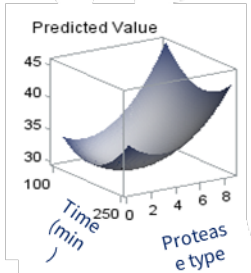


Optimization SRM

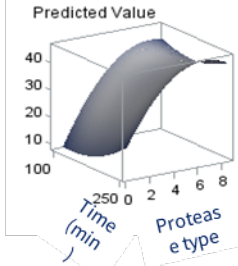
DPP-IV



α-Amylase



α-Glucosidase



- **Biochemical inhibition assays**
- **Cell culture appropriate for bioactivity**
- ***In vivo* animal and human studies**

***In silico* inhibition simulation**

Mojica, L., González de Mejia, E., Granados-Silvestre, M.A., Menjivar, M. 2017. J Functional Foods 31, 274-286.

UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

Protein Hydrolysates

Beneficial Effects:

1. Free amino acids are easily absorbed
2. Flavor enhancing (monosodium glutamate, MSG)
    a) Flavor enhancer – improves flavor w/o adding flavor itself
3. Protein hydrolysates – flavors
4. Carbonyl-amine browning – flavors

Loss of Quality:

1. Undesirable non-enzymatic browning
2. Enzymatic oxidation of phenolic substrates
    a) Example: tyrosine → DOPA (L-dihydroxyphenylalanine)
3. Deterioration of amino acids by microbes
4. Degradation of free glutamine – heat processing

Attributes to Assess Identity

- Degree of purification;
- Length/amino acid sequence and molecular heterogeneity;
- Secondary/tertiary structure and aggregation;
- Chemical and gastrointestinal stability;
- Specific bioactivity;
- Bioavailability;
- Immunogenicity/allergenicity;
- Acute, subchronic, and chronic toxicity;
- Impurities, contaminants, and process residues;
- ADMET studies
- Drug interactions;
- Synergism/antagonism with other ingredients;
- Batch-to-batch consistency;

Chalamaiah *et al*. (2019). Regulatory requirements of bioactive peptides (protein hydrolisates) from food proteins. *Journal of Functional Foods, 58,* 123-129.
Xu *et al*. (2019). Bioavailability of bioactive peptides derived from food proteins across the intestinal epithelial membrane: a review. *Trends in Food Science & Technology, 86,* 399-411.

Opportunities to Enhance Future Applications

Research to determine common quality attributes to assess and establish the **identity and consistency of proteins, peptides and enzymes**

Considering the **complexity** in the preparation of proteins, peptides and enzymes keep potential changes in functionality and **safety** in mind

Metabolomics and transcriptomics: to demonstrate the interaction, efficacy, and **mechanisms of action**

Novel processing technologies: to enhance the enzymatic release from parent proteins and produce **high yields** of food peptides

Product **development** and basis for **potential nutritional claims**

3rd International Symposium on Bioactive Peptides. *J. Agric. Food Chem.* 2024, 72, 43, 23709-23715.

Summary

- There is a variety of methods for the concentration/isolation of proteins and production of peptides, either from plant or animal origin.
- Depending on the method of production the identity of the produced ingredients may change their quality attributes.
- Some of the changes may be insignificant or adverse depending on the conditions.
- Depending on the method, there may be undesirable changes in the final product such as the chemical nature of the amino acids, bioaccessibility and bioavailability, interactions, sensory changes (bitterness).
- The most important quality attributes to establish identity are the functional and structural characteristics of the hydrolysate produced including amino acid content and sequence, degree of hydrolysis, physicochemical and technological properties and safety.
- Due to the complexity in the production of hydrolysates and peptides, standardization is unlikely to be attained.

March 27, 2026

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Industry Perspectives on Ingredient Identity

Linda Neckmar, SVP Human Health

FDA Public Meeting: Exploring the Scope of Dietary Supplement Ingredients
Session 3

Microbiology is at the heart of Novonesis

We leverage the power of our planet’s microbes, enzymes and functional proteins with our innovative technology, enabling healthier lives and a healthier planet.

Innovating across 30+ industries for people and planet

Our biosolutions are designed with safety at the forefront, ensuring regulatory readiness across regions and intended end uses.






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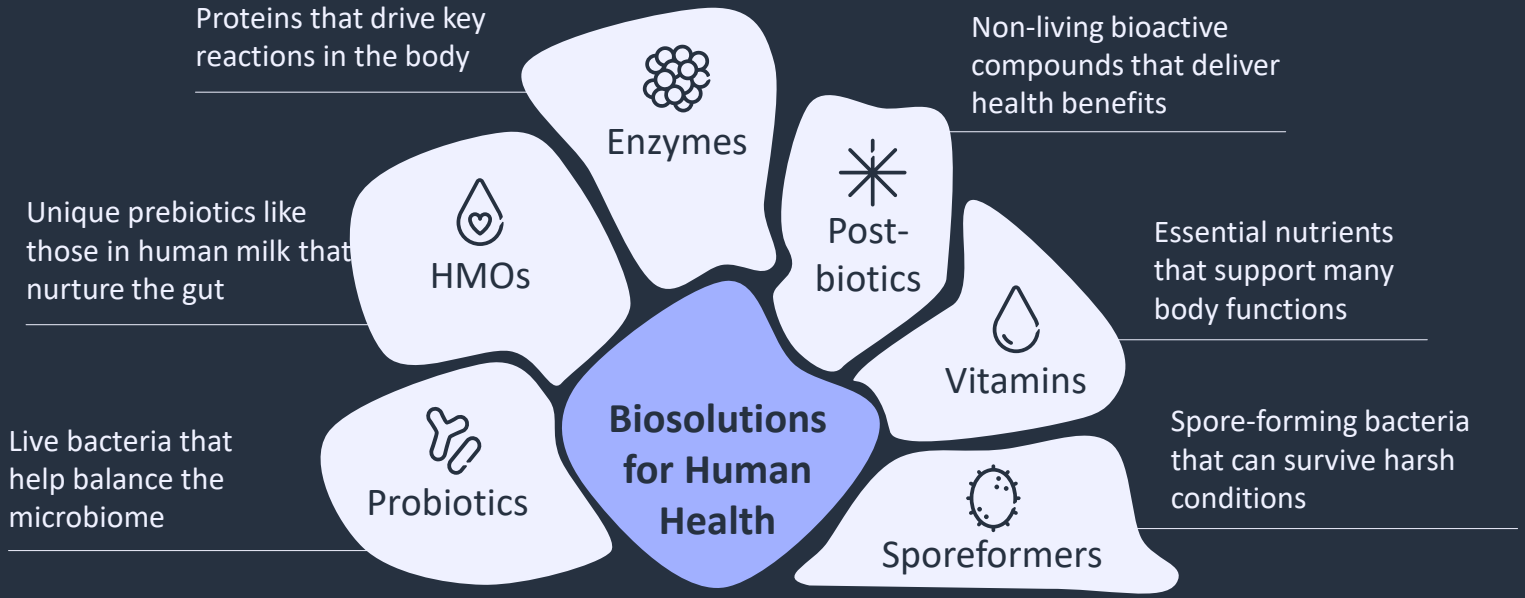
Human Health Biosolutions Categories



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The Challenge: Current interpretation of Clause (E)* as it relates to the identity of a substance unnecessarily restricts the NDIN pathway.

FDA's Questions	Proposed Approach	Why Alignment Matters
How should Clause (E) be interpreted for substances that have never been part of the diet?	Substances should not need to be isolated from a food, or be marketed in a conventional food, to qualify as a dietary ingredient.	Clear regulatory framework for NDIs will provide greater transparency and consumer confidence.
When is an ingredient's identity meaningfully altered, and what characteristic parameters should be considered?	Consideration should be made case-by-case, depending on the ingredient. Weight-of-Evidence approach should be applied.	Focus on meaningful risk factors helps prioritize safety-relevant data and streamline review

*Under the FD&C Act, a dietary supplement is a product containing one or more dietary ingredients, including: "*a dietary substance for use by man to supplement the diet by increasing the total dietary intake*" – Section 201(ff)(1)(E)

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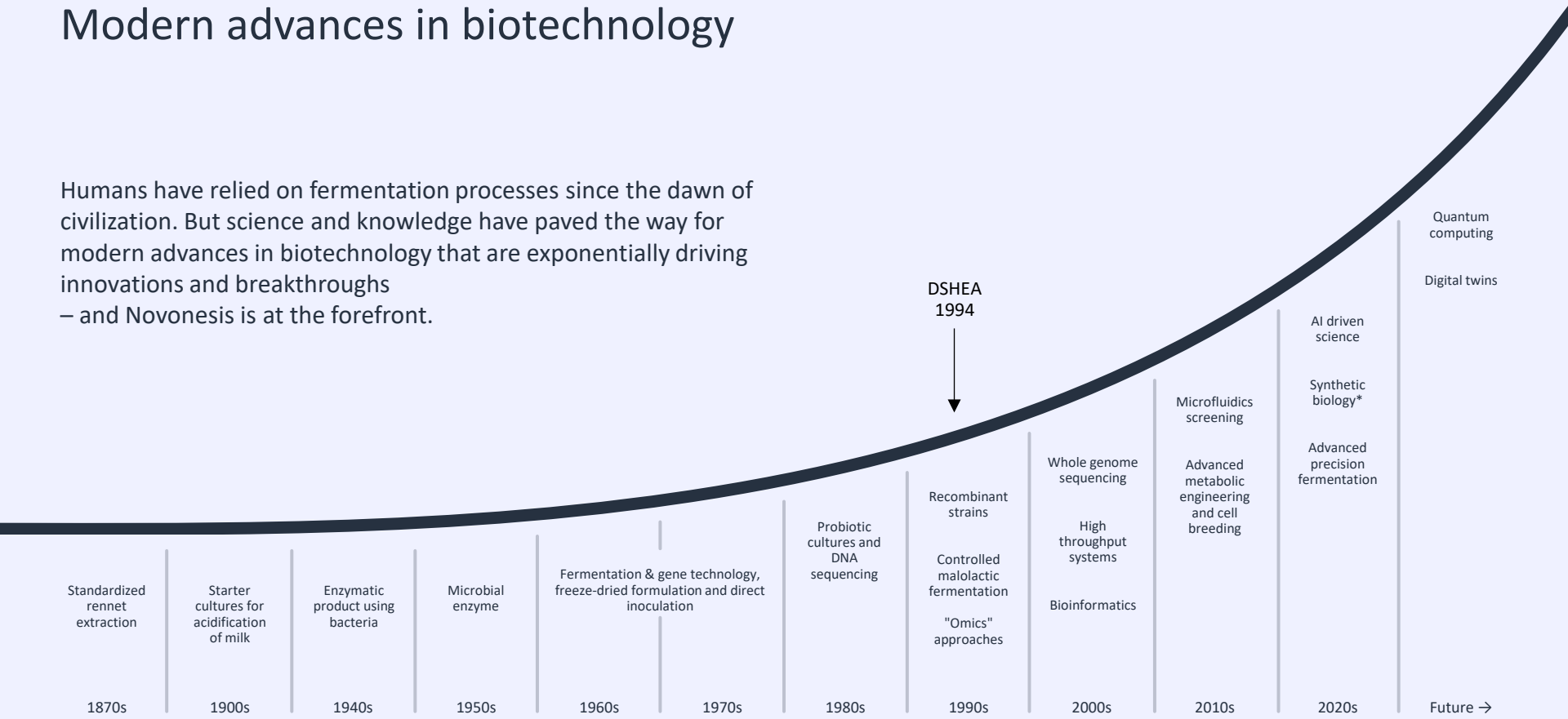
Modern advances in biotechnology

Humans have relied on fermentation processes since the dawn of civilization. But science and knowledge have paved the way for modern advances in biotechnology that are exponentially driving innovations and breakthroughs
– and Novonesis is at the forefront.



** Synthetic biology: A scientific term meaning the deliberate (re)design and construction of novel biological and biologically based systems for useful purposes.*

And what is precision fermentation protein?

Research & development

Target gene and protein

We test and design thousands of genes to identifying the ideal candidate for a protein application

Upstream

Production organism

Target protein gene is inserted into the microorganism

Fermentation

The microorganisms are fermented to produce the proteins by dosing sugar and other macro- & micronutrients

Downstream

Processing

The produced protein is separated from the microorganism after the fermentation has ended followed by further purification processes

Spray drying

The processed protein is spray dried into a powder format

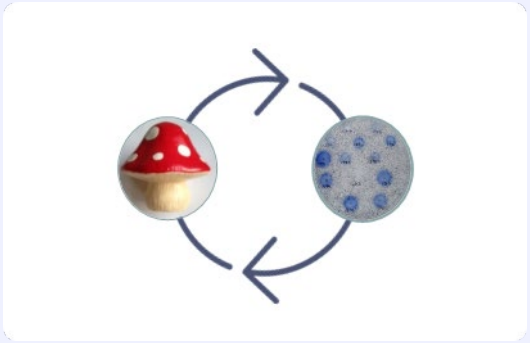
Market

Final product

The protein ingredient is sold in a final product within health and nutrition

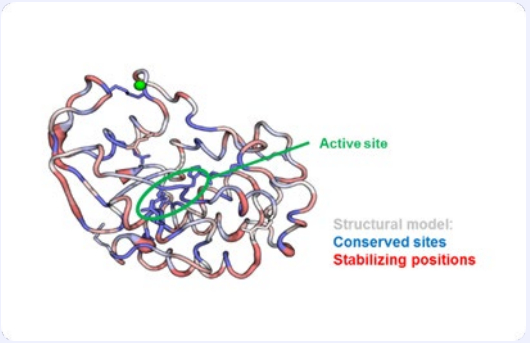
Biosolutions research

Microbial Discovery
Tapping into nature



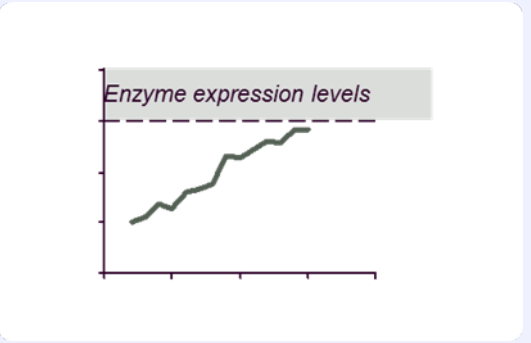
- Wild-type enzyme and microbe discovery
- Diversity insourcing via microbe isolation and DNA sequencing

Protein Optimization
Harnessing nature’s work



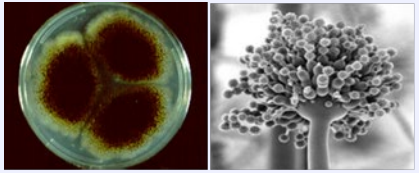
- Enzyme characterization through structural insight
- Parallelized variant screening
- Assay and screening system development

Production Strains
Reaching max potential

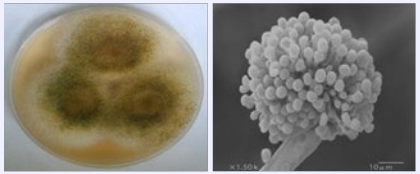


- Fungal and bacterial production strain construction and optimization
- Fermentation process development
- Automation technology development

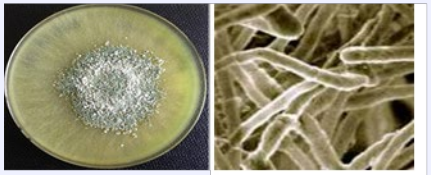
Examples of safe production strains across biosolutions



Aspergillus niger

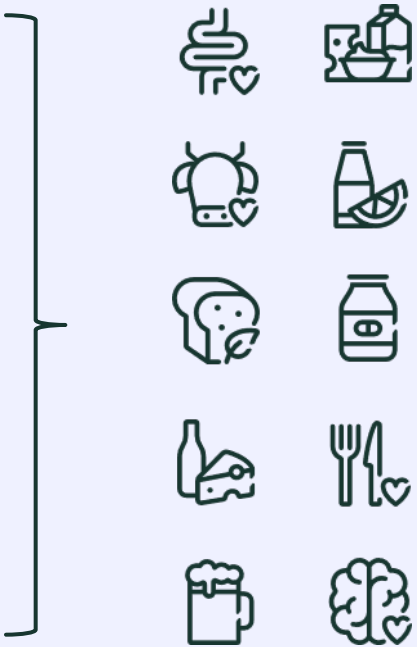


Aspergillus oryzae



Trichoderma reesei

Bacillus subtilis
Bacillus licheniformis



Microbial fermentation is currently the only feasible technology to produce Human Milk Oligosaccharides (HMOs) at a large scale and efficient cost

	Isolation from human milk	Chemical synthesis	Enzymatic synthesis	Microbial fermentation
+	• Theoretical option to isolate HMOs	• Synthesis of each HMO structure theoretically possible	• Synthesis of each HMO structure theoretically possible	• Synthesis of each HMO structure theoretically possible • **Large volumes of food-grade HMOs available**
−	• Difficult extraction • Contradictory to breastfeeding	• Large-scale, food-grade, production impossible	• Large-scale, food-grade production limited	• Need to ensure clear reg pathway is available for manufactured HMOs

A clearer regulatory framework is needed for New Dietary Ingredients

Narrow interpretation of Clause (E) unnecessarily excludes substances from the NDI notification pathway

Dataset to include in an NDI notification can be based on established safety paradigms (e.g., for substance classes)

Establishing a clearer regulatory framework will:

- **Promote successful NDIN submissions by developers**, making it easier for FDA to review products efficiently while increasing transparency for consumers
- Support **predictable and timely regulatory decisions**, helping ensure that safe products reach the market without unnecessary delay
- **Meet public health goals** by enabling access to safe, well-characterized ingredients that can contribute to improved nutrition and help address diet-related chronic diseases, in line with broader efforts to make Americans healthier

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Thank you

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Exploring the Scope of Dietary Supplement Ingredients

March 27, 2026

Identity Attributes: When Does ‘Sameness’ Matter?

Andrea W. Wong, Ph.D.

Senior Vice President & Chief Science Officer

Council for Responsible Nutrition

Just some of our members and their brands

CRN

“Responsible Innovation”

- **Does not limit dietary substances to only those that are identical to substances in the conventional food supply**
- **Innovation means new ingredients may be considered**
- **Responsible innovation means these new ingredients are safe for their intended use**

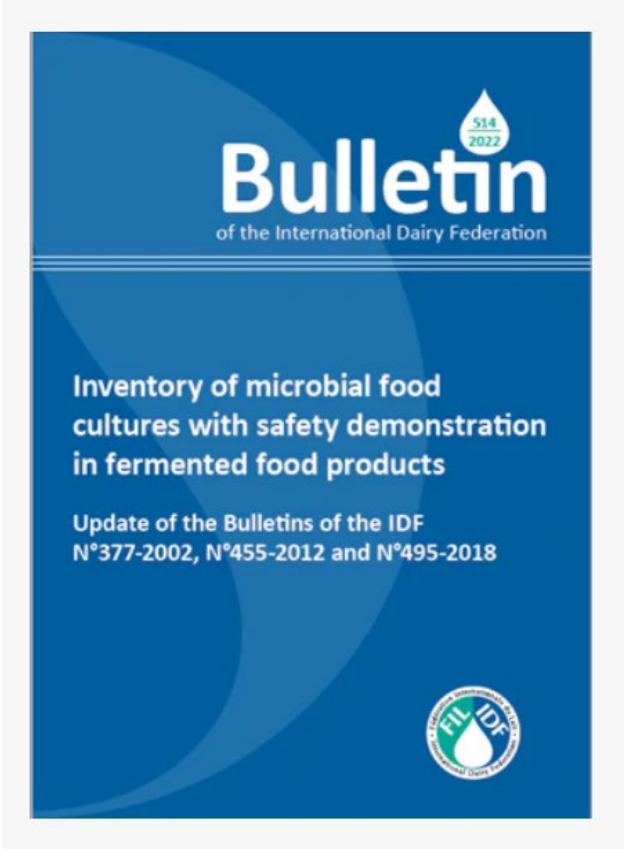
Responsible Innovation via NDIN

DSHEA requires that NDIs be notified to FDA unless the dietary ingredients "have been present in the food supply as an article used for food in a form in which the food has not been chemically altered."


KNOCK!
KNOCK!

"Your notification appears to contain numerous examples of historical and/or traditional consumption of the *[name]* species. Some references identify to the strain level while others do not; regardless, none of the references identify [strain number] as the strain being consumed."

"FDA was unable to establish the identity of your new dietary ingredient based on the information provided in your notification. For example, the notification did not provide adequate evidence showing that the proposed NDI is the same in protein-folding structure, post-translational modifications, enzyme stability, and enzyme activity to the native enzyme found in food. Additionally, the notification did not provide adequate documentation or analyses showing what other proteins from the manufacturing strain were present in the proposed NDI."



EFSA EUROPEAN FOOD SAFETY AUTHORITY

EN English Menu

Home / QPS assessment

Qualified presumption of safety (QPS)

"The QPS status of a certain taxonomic unit (TU) is granted through the QPS assessment at **species** level for bacteria, yeasts, bacteriophages and microalgae/protists and at family level for non-bacterial viruses, while the safety assessment of a MO notified through an application for market authorisation is done at strain level."

"(IDF) announced the publication of the updated inventory of microbial food cultures (MFC), with a demonstration of the safety of use in fermented foods…
"Readers will find a table inventory listing the **species** of microbial food cultures…"

For microbials:

At minimum,

- **Recognize that microbials identical to those present in the food supply at the species level are dietary substances**
- **Safety of the microbial for its intended use should be evaluated at the strain level as part of the NDIN submission**

Resources for determining safety

Regulatory Toxicology and Pharmacology 73 (2015) 164–171

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Determining the safety of microbial cultures for consumption by humans and animals

Michael W. Pariza [a, *], Kevin O. Gillies [b], Sarah F. Kraak-Ripple [c], Gregory Leyer [d], Amy B. Smith [c]

Regulatory Toxicology and Pharmacology 136 (2022) 105266

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Considerations for determining safety of probiotics: A USP perspective

Amy L. Roe [a, *], Marie-Eve Boyte [b], Chris A. Elkins [c], Virginia S. Goldman [d], James Heimbach [e], Emily Madden [d], Hellen Oketch-Rabah [d], Mary Ellen Sanders [f], Jay Sirois [g], Amy Smith [h]

Identity attributes matter…*for safety*

- **Proteins:** production method, amino acid sequence, post-translational modification, folding, activity
- **Enzymes:** source organism, fermentation media, activity
- **Microbials:** genomic sequence, metabolic characteristics, virulence factors, antibiotic resistance
- **‘Sameness’ is important for bridging safety information**

Thank you

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www.crnusa.org

Session 3: Identity Attributes of Microbial Dietary Ingredients

Gregory Leyer, PhD
Biotic Solutions Consulting LLC

Microorganisms Are Unique Dietary Ingredients

- Living, replicating biological entities

- Identity is defined across multiple levels of classification
  - Unlike chemical ingredients, microbial identity is determined through multiple layers of classification from genus and species down to the specific strain – each providing increasing resolution

- Multiple attributes define identity:
  - Taxonomic identity
  - Genomic identity
  - Strain lineage
  - Functional characteristics

Key Attributes Used to Establish Microbial Identity

- Genomic identity
  - Taxonomic classification
  - Whole genome sequence or strain markers
- Strain lineage
  - Cell banking, lineage control, and production practices ensure a match to the characterized reference strain
- Functional and safety attributes
  - Metabolic traits, virulence factors, antibiotic resistance
  - Confirm the organism behaves as expected

Microbial identity is determined through layers of classification, from genus and species down to strain and genomic lineage

Common Methods Used in Industry

- 16S rRNA gene sequencing for genus/species confirmation
- MALDI-TOF for rapid taxonomic identification
- Genomic fingerprinting or strain-specific PCR for strain resolution
- Whole genome sequencing (industry standard/regulatory requirement)
- Routine QC often uses targeted assays

Species vs. Strain: A Central Question

Lactobacillus	*acidophilus*	XXX
Genus	species	strain

- Microbial species may contain genomic diversity
- Two strains of the same species can differ in meaningful ways
- Clinical evidence for probiotics is typically strain-specific
- Strain designation provides a link to:
  - Safety data
  - Clinical evidence
  - Manufacturing lineage

Why Strain-Level Differences Matter

- Strains within a species can differ genetically
- Differences *may* influence:
  - Clinical activity
  - Safety characteristics
  - Metabolic outputs
- Example: *Lactocaseibacillus rhamnosus* strains (LGG® vs HN001 ® vs others) differ in clinical outcomes

Safety Differences Between Strains

- Rare species contain both safe and potentially harmful *strains*
- Exceptional Example:
  - *E. coli* as a probiotic or harboring enterotoxigenic genes
    - Strain *Nissle* vs. O157:H7
- Strain-level genomic analysis helps identify these differences

Challenges in Strain-Specific Identification

- Comparative genome datasets may be limited
- Bioinformatics expertise varies across industry
- Taxonomy continues to evolve
- Perfect strain-specific assays may not always be feasible

Intentional vs Incidental Microbial Presence

- Microorganisms may occur naturally in foods
- But not all occurrences represent intentional dietary substances
- Example: *L. curvatus*
  - *Incidental* (non-starter lactic acid bacteria; NSLAB) and beneficial in many fermented foods such as kimchi and sausage
  - *Intentional* strains are used as a protective cultures in the food industry (anti-Listeria effects)
  - *Incidental* presence may cause spoilage in vacuum-packed meats etc.
  - *Intentional* strain isolates may also have probiotic properties (ex. LB-P9)
- Context matters
  - Simply detecting a microorganism (genus/species) may ≠ dietary ingredient

IPA Does Process Optimization Change Microbial Identity?

- Fermentation processes often evolve to maximize yield, stability, etc.
- Examples: media composition, pH control, temperature, etc.
- These changes affect growth and yield
- But does NOT result in a chemical alteration

If the organism produced at the end of the process is the same strain, the identity of the ingredient has not changed.

Example: Changing fertilizer or soil conditions does not change the identity of the plant species.

Microbial Ingredients Represent a Unique Class of Ingredients

- **Key Takeaways**
  - Microbial identity differs from chemical ingredients
  - Strain-level characterization is linked to efficacy
  - Manufacturing changes do not alter identity
  - Safety is predominantly determined at the species level, with abbreviated confirmation at the strain level
  - Context matters when defining dietary substances

IPA

Thank You!

Gregory Leyer, PhD

Biotic Solutions Consulting LLC

www.ipa-biotics.org

greg@biotic-solutions.com

Public

Dietary Substances & the Identity of Probiotic Strains

Amy B. Smith, Ph.D.
Sr. Director of Medical Affairs, North America
Kerry ProActive Health

Public

Disclosures

International Probiotics Association
Current & Past President

Natural Products Association
Member

KERRY

Sr. Director of Medical Affairs, North America

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994 (DSHEA)
Section 2: Findings

- **Improving the health status** of US citizens ranks at the top of the national priorities of the Federal Government
- The importance of nutrition and the benefits of dietary supplements to **health promotion** and **disease prevention** have been documented increasingly in scientific studies

- There is a link between the ingestion of certain nutrients or dietary supplements and the prevention of chronic diseases such as cancer, heart disease, and osteoporosis; and clinical research has shown that several chronic diseases can be prevented…preventive health measures, including education, good nutrition, and appropriate use of safe **nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures**
- **Consumers should be empowered** to make choices about preventive health care programs based on data from scientific studies of **health benefits related to particular dietary supplements**

- The nutritional supplement industry is an integral part of the **economy of the US**
- Although the Federal Government should take swift action against products that are unsafe or adulterated, **the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers**

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994 (DSHEA)

Section 3: Definitions

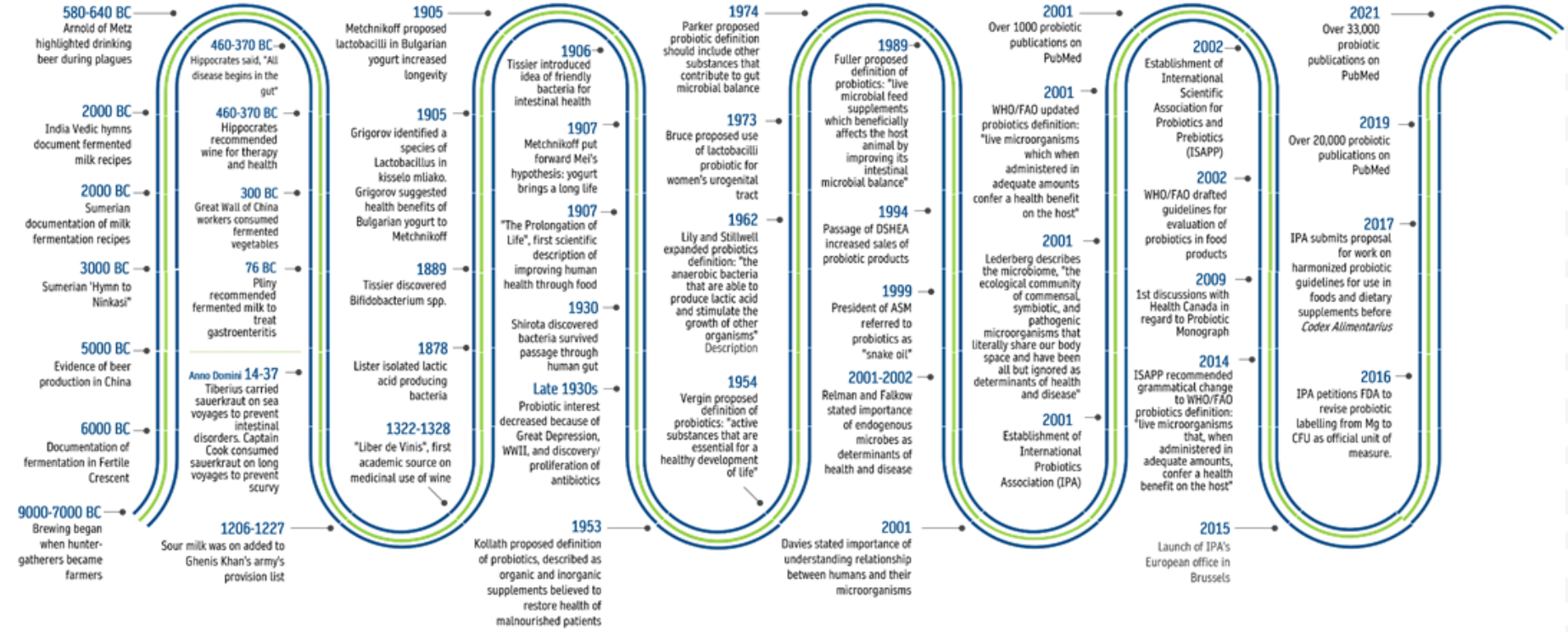
- DEFINITION OF CERTAIN FOODS AS DIETARY SUPPLEMENTS. SECTION 201 (21 USC 321) IS AMENDED BY ADDING AT THE END OF THE FOLLOWING:

(ff)THE TERM 'DIETARY SUPPLEMENT' –

1. Means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

   A. a vitamin
   B. a mineral
   C. an herb or other botanical
   D. an amino acid
   E. a *dietary substance* for use by man *to supplement the diet* by increasing the total dietary intake; or
   F. a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause A, B, C, D or E

Highlights from the History of Probiotics



Standardization Gap Across Dietary Ingredients

FDA's current interpretation of a 'dietary substance' includes only *intentional* constituents of food

A. VITAMINS **B.** MINERALS **C.** HERBS OR BOTANICALS **D.** AMINO ACIDS	SAFETY
E. A DIETARY SUBSTANCE FOR USE BY MAN *TO* SUPPLEMENT THE DIET BY INCREASING THE TOTAL DIETARY INTAKE	**MUST PROVE PRESENCE OF *STRAIN* IN THE "FOOD SUPPLY"**

SAFETY

SCIENTIFIC NOMENCLATURE & CHOOSING THE RIGHT STRAIN

Why precise strain identity matters

Standardized Nomenclature

Probiotic strains are classified by: Genus → Species → Strain; to ensure precise scientific identification

Genus	Species	Strain
Limosilactobacillus	*fermentum*	CECT5716 (LC40)
Limosilactobacillus	*fermentum*	XYZ-1A

SPECIES = SAFETY;
STRAIN = EFFICACY

Why Strain Identity Matters

- Safety characteristics (morphology, metabolism, physiology) are shared at the species level*
- Functional benefits and clinical efficacy differ at the strain level.

Analogy → Same Species, Different Performance

Genus	Species	Strain
Canis	*lupus familiaris*	German Shepherd
Canis	*lupus familiaris*	French Bulldog

Different dog breeds have different capabilities. Likewise, probiotic strains within the same species can have varying properties.

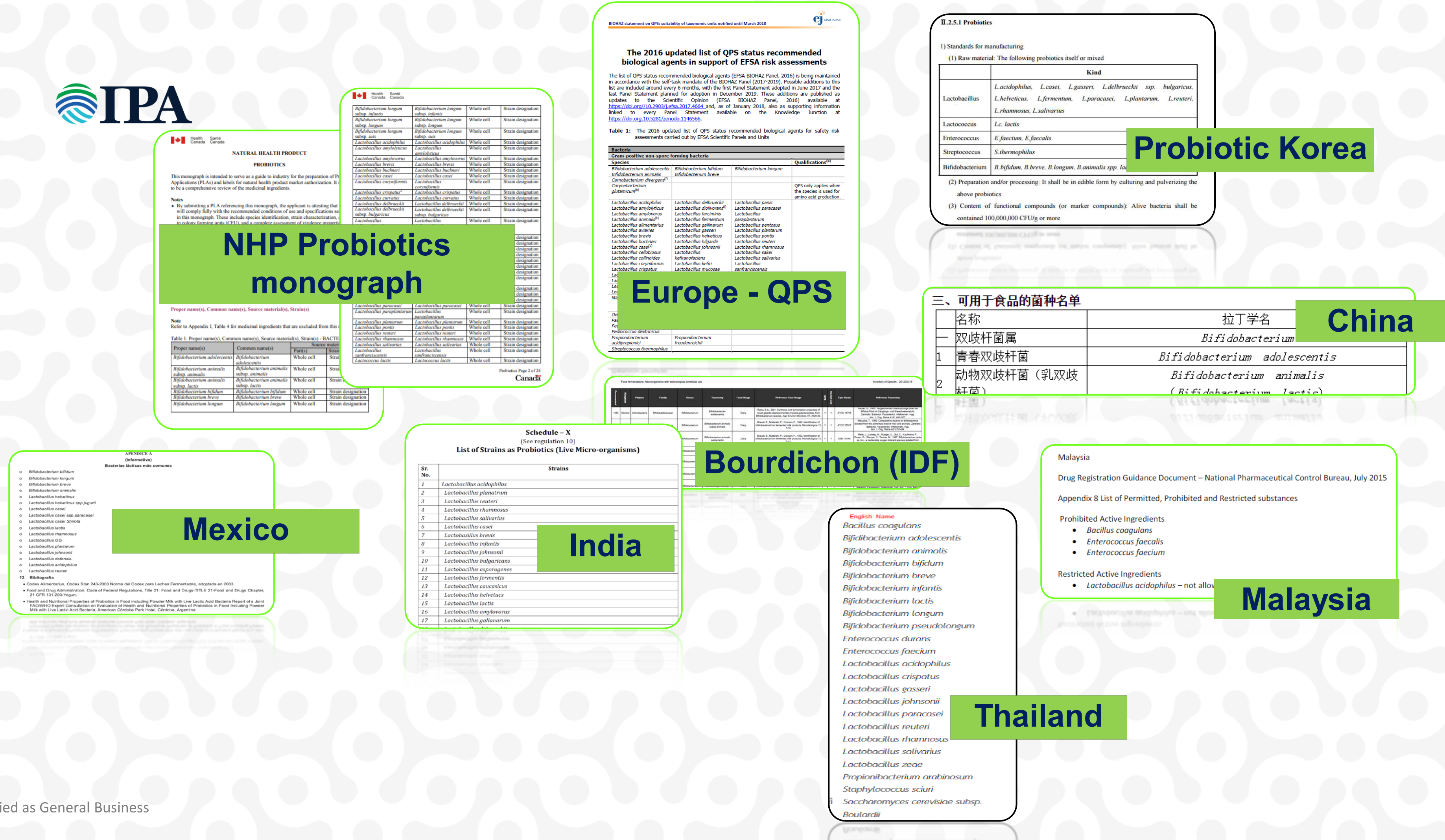
WOULD YOU CHOOSE A FRENCH BULLDOG TO BE YOUR GUARD DOG?

*Roe AL, Boyte ME, Elkins CA, Goldman VS, Heimbach J, Madden E, Oketch-Rabah H, Sanders ME, Sirois J, Smith A. Considerations for determining safety of probiotics: A USP perspective. Regul Toxicol Pharmacol. 2022 Dec;136:105266. doi: 10.1016/j.yrtph.2022.105266. Epub 2022 Oct 4. PMID: 36206977; PMCID: PMC10292223.

WHEN IS STRAIN SPECIFIC IDENTITY INFORMATION USEFUL?

- Evidence of a controlled manufacturing process (strain in, strain out)
- Clinical documentation of efficacy as demonstrated in clinical trials
- Supplement Facts Panel to correspond to structure/function language
- Identification of antibiotic resistance profile and lack of transfer potential
- Virulence factor mining in species with known pathogenic traits (i.e., pathogenicity islands)
- Intellectual Property

IPA



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1. Means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

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   D. an amino acid
   E. a *dietary substance* for use by man *to supplement the diet* by increasing the total dietary intake; or
   F. a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause A, B, C, D or E

Intentional and Incidental Presence of Live Microbials

GUT MICROBES
2025, VOL. 17, NO. 1, 2551113
https://doi.org/10.1080/19490976.2025.2551113

Taylor & Francis
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REVIEW ARTICLE

OPEN ACCESS Check for updates

Linking the edible plant microbiome and human gut microbiome

Gabriele Berg[a,b,c], Gerardo V. Toledo[d], Jasper Schierstaedt[a], Heikki Hyöty[e,f], and Wisnu Adi Wicaksono[a]

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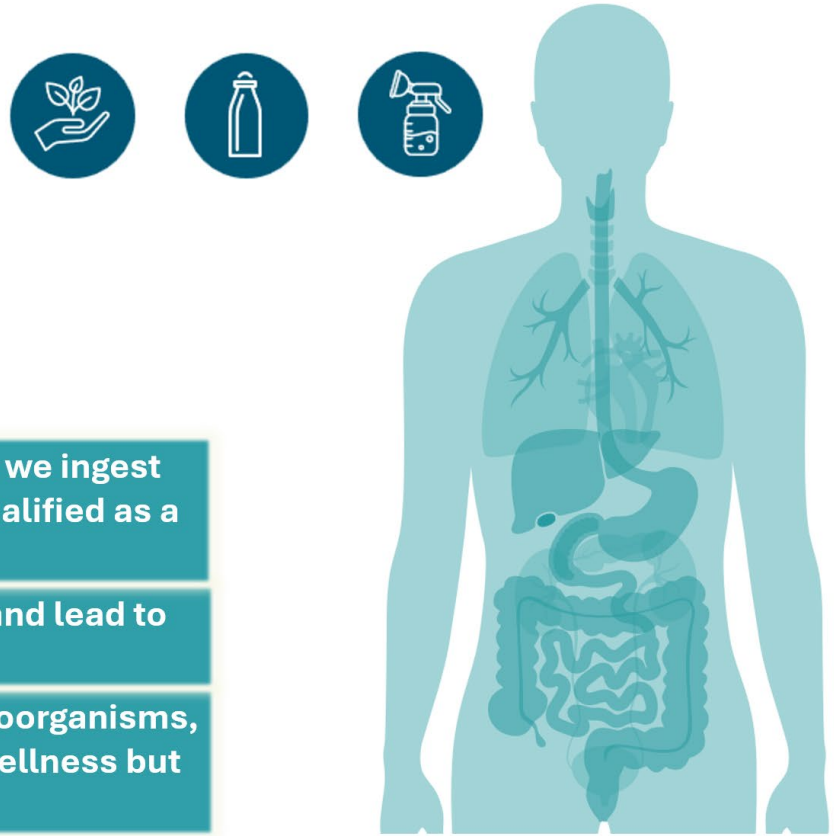
ABSTRACT

The edible plant microbiome, which includes microbes in raw-eaten plants, has been recently recognized as a vehicle delivering microbes to the gut. Fruits and vegetables can carry thousands to billions of microorganisms with diverse genetic capacities on each serving. Since the 'edible plant microbiome' concept was introduced in 2014, notable progress has been made in understanding its microbial diversity, factors influencing it, functional traits and biomarkers, and its interconnection with the human gut microbiome. The discovery of the link between microbes in plants consumed raw and the gut microbiome establishes a possible continuum from farm to fork and health.

KEYWORDS

Edible plant microbiome; gut microbiome; fruits and vegetables; human health



When we eat food that provide probiotics, the strains we ingest adapt to the environment of the GI tract and remain qualified as a dietary ingredient

Plant and soil microbes colonize the human GI tract and lead to enhanced microbial diversity

The human GI tract is comprised of trillions of live microorganisms, many of which have beneficial properties to provide wellness but not identified as part of the food supply.

Berg G, Toledo GV, Schierstaedt J, Hyöty H, Adi Wicaksono W. Linking the edible plant microbiome and human gut microbiome. Gut Microbes. 2025 Dec;17(1):2551113. doi: 10.1080/19490976.2025.2551113. Epub 2025 Sep 4. PMID: 40906895; PMCID: PMC12413042.

Incidental Microbes Shape our GI Microbiomes - *Providing Health & Wellness*

IPA

These microbes may be useful to supplement the diet of those who do not have access to fruits and vegetables!

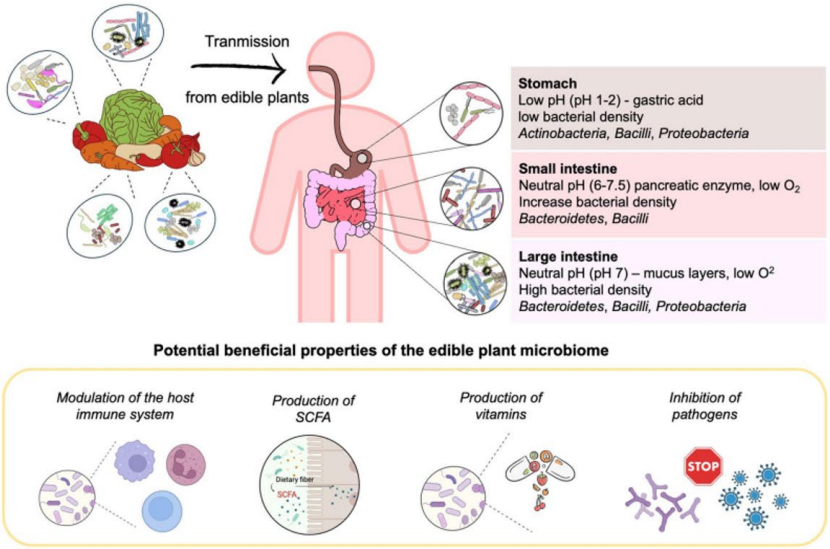
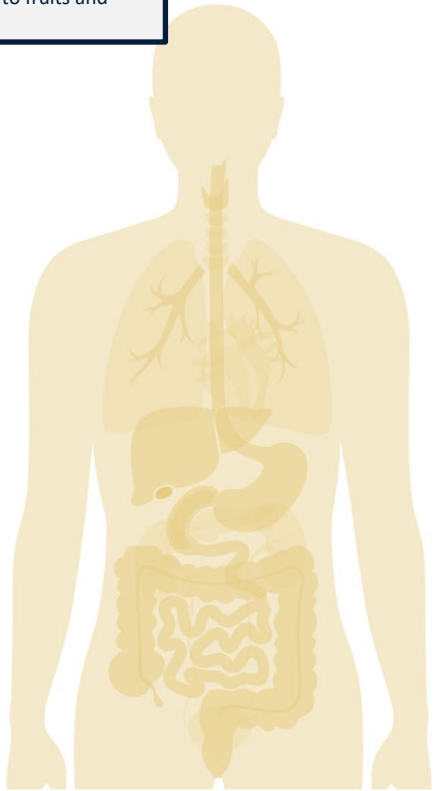


Figure 2. Microbial transmission from plants to the human gastrointestinal system and its potential implications for human health. This figure was created using Canva (https://www.canva.com.) and BioRender (https://biorender.com).



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Summary

- Currently there is an unfair, unfounded and unnecessary **regulatory burden** for dietary substances outside of pre-determined dietary ingredient status of vitamins, mineral, herbs/botanicals or amino acids.
- Subpart E was intended to provide an **innovation clause** as per DSHEA founders.
- Both intentional and incidental live microbes in the diet shape the healthy diversity of the human gut microbiome – **why limit probiotic benefits to consumers with only those strains in the "food supply"?**
- Probiotic species are currently recognized as appropriate for use in foods and dietary supplements by regulatory agencies globally with **strain-specific information needed only to justify safety when justification is required.**
- Modernization of the interpretation of dietary substance is needed to acknowledge the appropriate nature of probiotics as a category **to supplement the diet of those lacking beneficial microbes.**
- The origin of the probiotic is out of scope – **safety is the appropriate regulatory burden**.
- **Beneficial microbes comprise the gut microflora**, many of which are health-promoting and not intentionally added to the food supply.
- DSHEA findings indicate that dietary supplements are intended to **improve the health status of US citizens**, that consumers **should be empowered, and that the federal government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers.**
- **Probiotics are dietary substances which supplement the diet of US consumers, providing health and wellness.**

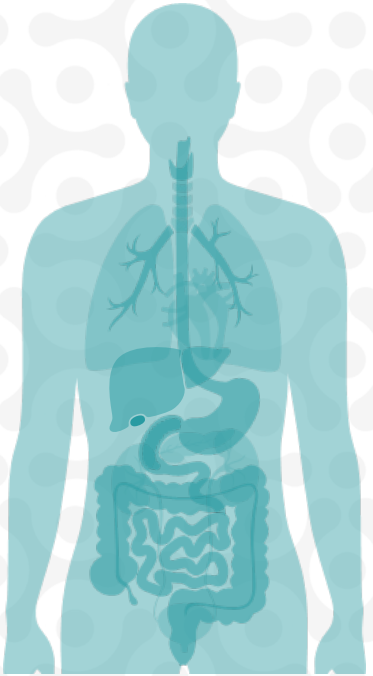
THE PRO-HEALTH ASK & GOALS

The ASK:

- 'Dietary Substance' should ideally be interpreted as substances *appropriate* for use in dietary supplements* and not restricted to the current food supply.
  - Limitation of dietary substances to those identified as present in the "food supply" is out of line with subpart E as an *innovation clause*.
- Implement a technical amendment to list probiotics as a recognized dietary ingredient within subpart E of 201(ff).
  - Probiotics meet criteria of a dietary substance despite their source.
  - Standardize the regulatory burden among dietary ingredients and dietary substances.

The GOALS:

- To allow the consumer to have access to modern-day microbiome science solutions that allow general well-being and restoration of the microbiome.
- To allow innovative ingredients isolated from the environment or healthy individuals to be considered for use in dietary supplements.



***Appropriate is a question of safety and intended use, meeting appropriate regulatory standards (NDI, labeling, etc)**

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Session 3 Reminders

There is some overlap in today's topics.

- Please keep your Q&A in-line with this session – Identity attributes for ingredient types (proteins, enzymes, and microorganisms)

During Q&A:

- Be sure to speak your remarks into the microphones.
- Introduce yourself with your name and organization

April 27th is the deadline for submission of comments to the docket (No. FDA-2026-N-2047).

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 3:
Question and Answer

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Session 4:
Open public comment

Moderator: Cara Welch, Director, ODSP, HFP, FDA

FDA Panelists:
Shontell Wright, Chemist, ISB, DRE, ODSP, HFP, FDA
Betsy Jean Yakes, Identity and Status Branch Chief, DRE, ODSP, HFP, FDA
Phil Yeager, Director of Research and Evaluation, ODSP, HFP, FDA

Public Meeting: Exploring the Scope of Dietary Supplement Ingredients

Thank you for attending!

Docket No. FDA-2026-N-2047
Docket is open for comment until April 27, 2026


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