Council for Responsible Nutrition
1828 L Street, NW, Suite 220 • Washington, DC 20036-5114
(202) 204-7700 • www.crnusa.org

April 27, 2026

By Electronic Submission

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Public Meeting Exploring the Scope of Dietary Supplement Ingredients. Docket No. FDA-2026-N-2047.

The Council for Responsible Nutrition (CRN)[1] appreciates the opportunity to provide additional comments to the Food and Drug Administration (FDA) related to the Public Meeting Exploring the Scope of Dietary Supplement Ingredients held on Mar. 27, 2026. CRN participated as a presenter and offered oral remarks during the meeting. These comments expand upon the key issues discussed.[2]

A central topic raised during the meeting is which substances meet the statutory definition of a "dietary ingredient." Related issues include how new production methods affect ingredient identity and safety, and how to establish identity for emerging ingredient categories—such as proteins, peptides, enzymes, and microbials—that are not explicitly listed in the Federal Food, Drug, and Cosmetic Act (FDCA) but may fall within the category of "dietary substances."

---

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing the dietary supplement and functional food industry. Bringing together manufacturers, ingredient suppliers, and service providers, CRN unites its member companies around a shared commitment to science, transparency, and responsible business practices—advancing a strong, credible marketplace that supports consumer health and industry growth. Through strategic advocacy, self-regulatory leadership, voluntary guidelines, and evidence-based communications, CRN ensures that responsible companies are recognized, protected, and positioned to innovate and compete. Learn more at crnusa.org.

[2] FDA. Public Meeting Exploring the Scope of Dietary Supplement Ingredients. Available from: https://www.fda.gov/food/workshops-meetings-webinars-food-and-dietary-supplements/public-meeting-exploring-scope-dietary-supplement-ingredients-03272026#Meeting%20Information.

A dietary supplement is a product intended to supplement the diet that, among other requirements, contains one or more "dietary ingredients." Under section 201(ff)(1) of the FDCA, a dietary ingredient includes 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).

In recent decades, FDA has interpreted "dietary substance" in 201 (ff)(1)(E) narrowly, limiting it to substances previously marketed in conventional food. This interpretation, reflected in draft guidance to industry on new dietary ingredient (NDI) notifications,[3] has prevented certain innovative ingredients from qualifying as dietary substances and therefore from undergoing NDI safety review. As a result, the pathway intended to evaluate safety has instead become a barrier to innovation.

CRN is encouraged by FDA's recent recognition that longstanding interpretations may warrant reconsideration. As noted by the Deputy Commissioner for Human Foods, Kyle Diamantas, dietary supplements play an important role in addressing nutrient gaps and supporting health, yet the regulatory framework has not kept pace with scientific and technological advances. A modernized approach should remove unnecessary barriers to innovation while promoting regulatory clarity and strengthening public health protection. A restrictive interpretation of "dietary substance" undermines this goal by limiting the development of new ingredients, reducing FDA oversight, and restricting consumer access to beneficial products.

1. FDA's Interpretation of "Dietary Substance" is Inconsistent with the Statute

For more than a decade, CRN has consistently engaged with FDA on a fundamental question under the Dietary Supplement Health and Education Act (DSHEA): what Congress intended by the term "dietary substance" in section 201(ff)(1)(E) of the FDCA (see CRN's previous comments).[4] This provision is recognized as the "innovation clause" because it

[3] Draft Guidance for Industry: New Dietary Ingredient Notifications and Related Issues. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues. This draft guidance was originally issued in 2011, revised in 2016, and partially finalized in 2024. FDA has yet to finalize the parts on NDI identity and safety.
[4] CRN Comments on FDA's Responsible Innovation in Dietary Supplements Public Meeting (2019). Available from: CRN Comments_FDA Responsible Innovations Dietary Supplements Written_FINAL.pdf; CRN comments on Revised NDIN Draft Guidance (2016). Available at: CRN Comment_Revised NDI Draft Guidance_12December2016.pdf; CRN comments on Defining a "Dietary Ingredient (2011). Available at: https://www.crnusa.org/sites/default/files/pdfs/Appendix%20A_CRN_CHPA%20Comments_NDI%20Notification%20Draft%20Guidance_12-2-2011.pdf.

was intended to anticipate and accommodate growth of ingredient types and the dietary supplement marketplace, not to set artificial limits bound to the conventional food supply.

Our position has remained clear and consistent—grounded in the statutory text, structure, and legislative history.

Congress enacted DSHEA in 1994 as an amendment to the FDCA to ensure a suitable balance between maintaining consumer access to a wide variety of dietary supplements and providing FDA with appropriate oversight of the safety of dietary supplements and ingredients.

The plain language of DSHEA supports a broad and flexible understanding of "dietary substances." Section 201(ff)(1)(E) of the FDCA defines a dietary ingredient to include a "dietary substance for use by man to supplement the diet by increasing total dietary intake." The statutory text is unambiguous and deliberately broad. It contains no requirement that a dietary substance be present in, or previously marketed in, the conventional food supply.

FDA's longstanding interpretation—limiting "dietary substance" to substances with a history of use in conventional food—adds a condition that does not appear in the statute. This interpretation is inconsistent with basic principles of statutory construction and exceeds FDA's authority by effectively rewriting the definition enacted by Congress.

The more expansive interpretation is further reinforced by the functional language Congress selected. Terms such as "for use by man to supplement the diet" and "increase total dietary intake" are defined by intended use, not by source or historical consumption. FDA's interpretation, which effectively imposes a historical food-use requirement, substitutes a source-based limitation for the intended-use standard reflected in the statute.

Where Congress intended to impose a historical use requirement, it did so expressly. Section 413 of the FDCA conditions exemption from NDI notification on presence in the food supply. The absence of comparable language in section 201(ff)(1)(E) is dispositive.

Section 413 of the FDCA defines a dietary ingredient not marketed in the United States before October 15, 1994 as new, and requires FDA notification unless the ingredient is "present in the food supply as an article used for food in a form in which the food has not been chemically altered." Thus, NDIs present in the food supply are exempt from

notification. The 75-day pre-market notification process for NDIs not already present in the food supply requires the manufacturer to submit to FDA the information on which the manufacturer determined the safety of the dietary ingredient.

Congress did not include limitations or any requirement for historical use of a substance to supplement the diet under Section 201(ff)(1)(E), and FDA may not import requirements from one provision into another where Congress chose not to do so.

2. Legislative History Confirms a Broad, Innovation-Forward Definition

The legislative history of DSHEA confirms that Congress intended "dietary substance" to function as an expansive, forward-looking category.

Congress deliberately adopted a "catch-all" provision to ensure that emerging ingredients— including those developed through scientific advancement—would fall within the definition of dietary ingredients. The shift from "nutritional substances" in earlier drafts of DSHEA to "dietary substances" reflects this intent. [5]

Contemporaneous examples cited by Congress,[6] including coenzyme Q10, glucosamine, and primrose oil, further demonstrate that the definition was not limited to conventional food constituents and was intended to encompass synthesized or otherwise novel substances.

FDA's current interpretation is therefore not only unsupported by the statutory text, but also contrary to Congressional intent.

3. FDA's Interpretation Undermines the NDI Framework Established by Congress

FDA's restrictive interpretation has practical regulatory consequences that are inconsistent with DSHEA. Responsible industry prioritizes safety and uses the NDI notification process to provide FDA with premarket safety information. However, when FDA excludes

[5] Senate Report from Committee on Labor and Human Resources to Accompany S. 784 (DSHEA), Senate Report No. 103-410, at 8-9 (Oct. 8, 1994). CRN is aware that in an unprecedented move, at the signing of the bill certain members of Congress attempted to disclaim the legislative history of DSHEA, including the Senate Report. Congressional Statement of Agreement on DSHEA. 140 Cong. Rec. 14801 (daily ed. Oct.7, 1994). However, this attempt to disclaim the legislative history does not in fact change the legislative history or its importance for the interpretation of DSHEA.
[6] *Id*.

substances from qualifying as "dietary ingredients," companies are effectively shut out of the NDI pathway—preventing FDA from reviewing safety data altogether.

When access to the NDI pathway is restricted, firms may be compelled to pursue alternative pathways—such as introducing substances into the conventional food supply through the Generally Recognized as Safe (GRAS) pathway —to establish eligibility.

Many NDIs are intended specifically for dietary supplements and may target defined populations or use conditions that fall outside the GRAS paradigm. Requiring reliance on GRAS in these circumstances is inconsistent with the structure and purpose of DSHEA, which establishes a distinct regulatory pathway for dietary ingredients. Restoring a more expansive definition of "dietary substance," as DSHEA intended, would reduce the necessity for companies to pursue the GRAS pathway instead.

Congress established the NDI notification framework precisely to allow FDA to evaluate the safety of new dietary ingredients. FDA's interpretation instead creates a threshold barrier that precludes FDA's visibility into supplement-specific uses of novel ingredients, undermining both regulatory oversight and public health.

FDA should ensure that the NDI pathway remains accessible for all qualifying dietary ingredients, as intended under DSHEA. Revising the agency's interpretation of "dietary substance" is essential to restoring this pathway.

4. Innovation in Manufacturing Should Not Disqualify Ingredients

In the more than 30 years since DSHEA's enactment, advances in manufacturing, including synthesis, cell culture, and precision fermentation, have enabled production of safe, consistent, high-quality ingredients. These methods often improve purity without altering the fundamental identity or safety of the ingredient.

Advanced technologies allow production to occur efficiently in controlled systems. Current analytical tools allow verification that the desired product is manufactured. For example, precision fermentation is used to produce certain proteins, including enzymes, peptides, as well as bioactive metabolites and compounds traditionally sourced from botanical and other materials. Critical aspects, such as host selection, growth media, post-translational modifications, and filtration can be specified and controlled to ensure safe, consistent, and high-quality products that meet desired specifications without undesired impurities, such as host organisms, fermentation media, and allergens.

The impact of manufacturing changes should be assessed on a case-by-case basis, using specifications for the dietary ingredient as the basis for analysis. Regulatory evaluation should focus on whether manufacturing changes materially affect identity or safety. When no significant changes occur, companies should have access to efficient mechanisms (e.g., meetings with FDA) to confirm continued compliance. CRN notes that FDA previously addressed how to evaluate the effects of significant manufacturing changes for food ingredients and other substances in guidance.[7] This document could help companies assess similar changes for dietary ingredients.

5. Clarifying Identity for Emerging Ingredient Categories

In recent decades, many new ingredient innovations have been in non-traditional types such as proteins, peptides, enzymes, and microbials, which should fall under "dietary substance" in section 201(ff)(1) of the FDCA. For these ingredients, identity specifications can be established, and appropriate techniques can be applied for verification. For example, in the case of proteins, identity attributes include degree in purification, length/amino acid sequence, secondary/tertiary structure, specific bioactivity, post-translational modification, etc. Identity can be verified using N-terminal sequence, peptide mapping, bioassay, and isoelectric focusing. Identity attributes for microbials include taxonomic classification, strain lineage, metabolic traits, etc. Common methods used to determine microbial identity include 16S RNA gene sequencing (genus/species), genomic fingerprinting or strain-specific PCR, whole genome sequencing, and targeted assays.

Despite this rigor available to identify ingredients, companies have faced situations where FDA declines to review safety because the ingredient is deemed not to qualify as a dietary ingredient—often due to its lack of presence in the food supply. [8,9,10] This prevents scientific evaluation of safety and creates unnecessary regulatory uncertainty.

---

[7] 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. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-assessing-effects-significant-manufacturing-process-changes-including-emerging.
[8] NDI 1375 - Alternansucrase from Advanced Enzyme Technologies Ltd. Available from: https://www.regulations.gov/document/FDA-2025-S-0023-0011.
[9] NDI 1418 - Concentrated Nutriterra Omega-3 from Nuseed Nutritonal US Inc. Available from: https://www.regulations.gov/document/FDA-2025-S-0023-0093.
[10] NDI 1407 - Heat-treated culture of Bifidobacterium longum CBi0703 from Biose Industrie. Available from: https://www.regulations.gov/document/FDA-2025-S-0023-0071.

The appropriate regulatory approach is to allow such ingredients to proceed through the NDI framework, where identity and safety can be evaluated on the merits.

6. Refocusing "Sameness" on Safety, Not Eligibility

To the extent FDA relies on "sameness" to substances in the food supply as an eligibility threshold requirement, that approach improperly conflates eligibility with safety. Similarity may be relevant in evaluating safety on a case-by-case basis, but it is not a statutory prerequisite for qualification as a dietary ingredient. The governing inquiry remains whether the substance is intended to supplement the diet and whether it meets the applicable safety standard.

The safety standard for new dietary ingredients under DSHEA is "reasonable expectation of safety" under the conditions of use.[11] Considerations such as source, production method, and similarity should inform safety—not eligibility. This approach is especially important for innovative ingredients—including synthetic botanical constituents, microbials, enzymes, peptides, and bioactive compounds—that may not exist in the food supply but are intended to supplement the diet.

As an example, when examining the safety of a new microbial, it is important to identify the strain through whole genome sequencing and to understand whether there is history of use of microbials in the same species and to what extent the new strain is similar or different. Considerations include whether the microbial has Qualified Presumption of Safety (QPS) status,[12] which ensures that qualified experts have determined the microbial's genus and species to be safe for humans and animals based on assessment of taxonomic identity and related body of knowledge and potential safety concerns. At the strain level, it is necessary to determine lack of antibiotic resistance, transfer potential, toxin production, and virulence factors.[13] For strains within species that have little or no history of use, additional studies may be necessary depending on the specific substance.[14]

---

[11] 21 U.S.C. 350b(a)(2).
[12] EFSA. Qualified Presumption of Safety (EFSA). Available from: https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps.
[13] 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.
[14] EFSA Scientific Committee, Bennekou SH, Allende A, Bearth A, Casacuberta J, Castle L, Coja T, Crépet A, Halldorsson TI, Hoogenboom R, Jokelainen P, Knutsen HK, Lambré C, Nielsen SS, Turck D, Civera AV, Villa RE, Zorn H, Gómez MA, et al; Glandorf B. Guidance on the characterisation of microorganisms in support of the

FDA's current approach improperly conflates eligibility with safety and imposes an extra-statutory requirement that excludes otherwise lawful dietary ingredients.

7. FDA Should Modernize All Aspects of NDI Regulation

As FDA's full draft guidance on NDI notifications and related issues was released a decade ago, it is necessary to consider updates to the entire guidance with the modern lens. For example, in parallel with advances in ingredient manufacturing and characterization, toxicological science has progressed substantially, with non-animal, new approach methodologies (NAMs) and Next Generation Risk Assessment (NGRA) now forming an integral part of state-of-the-art scientific approaches to food, drugs, cosmetics and chemical ingredient safety assessments that are increasingly used across multiple FDA programs.

Recommendations in the draft NDI guidance continue to emphasize traditional in vivo testing strategies (e.g., 14-day range finding, 90-day sub-chronic, reproductive and developmental studies), which are no longer the sole, or always the most scientifically appropriate means of establishing reasonable assurance of safety.

FDA should therefore take this opportunity to recognize explicitly the role of fit-for-purpose non-animal NAMs, applied within the weight of evidence in the NGRA framework[15] to address specific safety questions relevant to dietary ingredients. CRN notes that an interagency coordinating committee has issued a strategic roadmap for establishing new approaches to chemical safety evaluation, which could serve as a useful reference.[16] Promoting robust and human relevant, non-animal safety assessments would ensure that the NDI guidance reflects current scientific capabilities and FDA policy direction.

---

risk assessment of products used in the food chain. *EFSA J.* 2025;23(11):e9705. doi:10.2903/j.efsa.2025.9705.

[15] Cable S, Baltazar MT, Bunglawala F, et al. Advancing systemic toxicity risk assessment: Evaluation of a NAM-based toolbox approach. *Toxicological Sciences*, Volume 204, Issue 1, March 2025, Pages 79–95, https://doi.org/10.1093/toxsci/kfae159.

[16] ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods). 2018. A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. Available: https://ntp.niehs.nih.gov/go/iccvam-rdmp. https://dx.doi.org/10.22427/NTP-ICCVAM-ROADMAP2018.

8. Effective Enforcement Promotes Overall Compliance with Premarket Notification

Effective enforcement of the NDI provision is critical to improving industry compliance and advancing FDA's public health mission. We emphasize that final NDI guidance providing clarity to industry would be necessary for enforcement. CRN recognizes the agency's resource constraints and has consistently supported increased funding for the Office of Dietary Supplement Programs.

FDA should take action when firms fail to submit NDI safety information at least 75 days before marketing when legally required. The agency should also commit to using the full range of available enforcement tools from warning letters to injunctions.

CRN recognizes that FDA needs enhanced technological tools to support more effective and targeted enforcement. A Mandatory Product Listing (MPL) framework—requiring dietary supplement manufacturers to submit key information such as company contact details, product labels, and ingredient lists—would improve FDA's visibility into the marketplace.

CRN supports the concept of a Mandatory Product Listing. We anticipate that if such a concept were to move forward to creation, CRN would fully participate in the discussions regarding its framework and implementation.

Consistent and escalating enforcement will send a clear signal that compliance with the NDI provision is mandatory. It will also reinforce FDA's support for responsible companies that follow the law to bring safe, innovative ingredients to market.

Conclusion

FDA should revise its interpretation of "dietary substance" in final guidance on NDI notifications to align with the plain language, structure, and legislative history of DSHEA. Updates to FDA communications about dietary supplements, including information on its website,[17] would also be warranted.

A legally sound interpretation would:

- Recognize that no food-use history is required under section 201(ff)(1)(E);

[17] FDA. Questions and Answers on Dietary Supplements. Available from: https://www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements.

- Ensure that qualifying ingredients can access the NDI notification pathway;
- Restore the statutory framework intended by Congress; and
- Support innovation while maintaining FDA's ability to evaluate safety.

Removing unnecessary barriers to the NDI process advances both public health and regulatory efficiency. FDA now has an opportunity to modernize its approach in a way that aligns with DSHEA's intent and today's scientific landscape.

Thank you for your consideration.

Sincerely,

Andrea Wong
Senior Vice President and Chief Science Officer

Megan Olsen
Senior Vice President and General Counsel

Haiuyen Nguyen
Vice President, Regulatory & Nutrition Policy