CIRS

Global Expert in New Food Ingredient Registration

# Guide to U.S. New Dietary Ingredient (NDI) Notification

## Global Expert in New Food Ingredient Registration

**U.S. Local Team:** Based in Virginia, our U.S. team includes full-time food regulatory and toxicology experts, including 2 DABTs, 1 ERT, and 24 DCSTs. We support clients with U.S. compliance services covering FDA GRAS, NDI, CAP, Animal Food GRAS, FDA AFIC, and AAFCO SRIS.

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# Chapter 1: Compliance Pathways for Food Ingredients in the United States

Pursuant to Sections 201(s) and 409 of the U.S. Federal Food, Drug, and Cosmetic Act (FD&C Act), any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA. Unless qualified experts unanimously agree that the substance is generally recognized as safe (GRAS) under its intended conditions of use, or the substance's use does not fall under the definition of a food additive (for example, substances meeting the definition of pesticides, dietary ingredients in dietary supplements, color additives, new animal drugs, or substances authorized or approved for use prior to September 6, 1958, are excluded from the definition of food additives).

Based on the legal framework above, compliance for new food ingredients in the United States currently follows four primary pathways:

1. Food Additive Petition (FAP)
2. Color Additive Petition (CAP)
3. Generally Recognized as Safe (GRAS)
4. New Dietary Ingredient Notification (NDIN, NDI notification)

The first three pathways apply to conventional food ingredients in the United States, while the NDI notification pathway applies to dietary supplement ingredients, which have their own unique regulatory framework. The main characteristics of these four pathways are as follows:

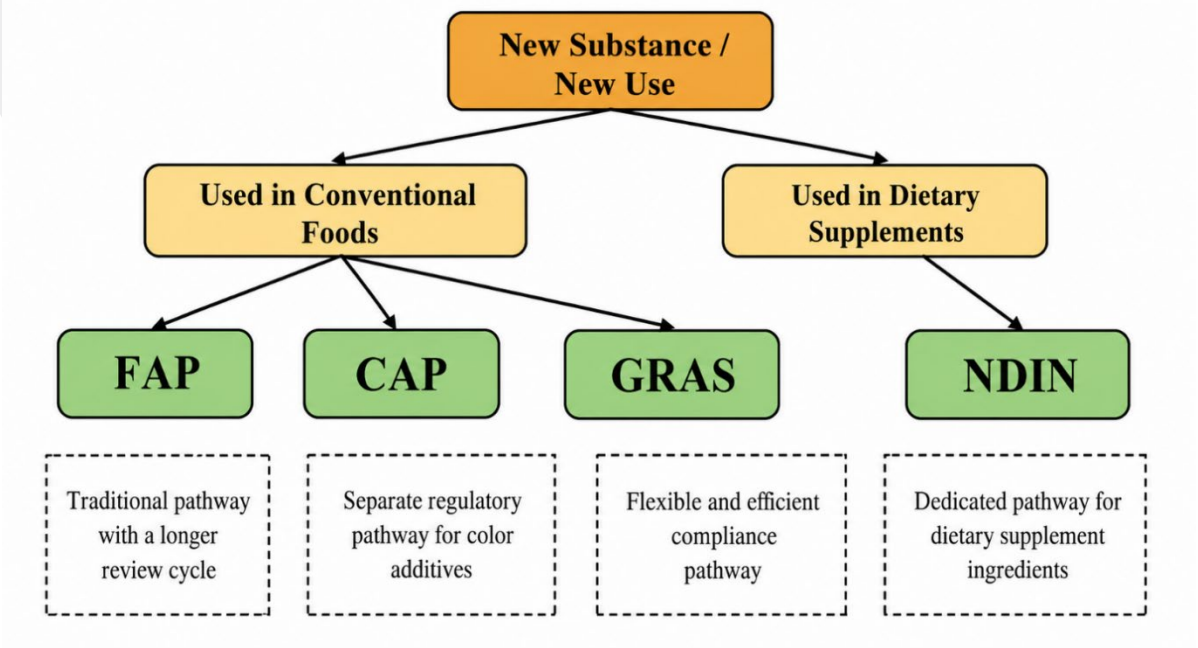


**Figure 1-1: Major Compliance Pathways for New Food Ingredients in the United States**

# Chapter 2: Regulatory Background of the U.S. NDI Notification

On October 25, 1994, the U.S. Dietary Supplement Health and Education Act (DSHEA) officially took effect. This Act amended the FD&C Act by adding several new provisions, including definitions and requirements for dietary supplements and new dietary ingredients, thereby establishing a new regulatory framework for dietary supplements in the United States.

## 2.1 Definition of Dietary Supplements

According to Section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)), a dietary supplement in the United States is 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 (A), (B), (C), (D), or (E) above.

Such products are ingested in the form of a tablet, capsule, powder, softgel, gelcap, or liquid, and are not represented for use as a conventional food or as a sole item of a meal or the diet.

Furthermore, this section stipulates that dietary supplements shall not include the following ingredients, unless the substance has previously been marketed as a dietary supplement or a general food product:

a) Substances approved as new drugs, antibiotics, or biologics;

b) Substances under investigation as new drugs, antibiotics, or biologics that have undergone extensive clinical research, and the existence of such research has been made public.

## 2.2 New Dietary Ingredients (NDI)

A new dietary ingredient (NDI) is a dietary ingredient that meets the definition of dietary ingredient described in Section 2.1 above and that was not marketed in the United States in a dietary supplement before October 15, 1994.

Note: To date, there is no officially authorized list of Pre-DSHEA dietary ingredients (i.e., dietary ingredients that were already on the U.S. market prior to October 15, 1994). Some unofficial U.S.

# Chapter 3: Current Status of NDI Notifications Under the

## 3.1 List of NDI Notification Data

The U.S. FDA has compiled a data inventory of NDI notifications submitted to the FDA since 1995. The publicly available information can be accessed on the FDA website.

| New Dietary Ingredient Notification # | New Dietary Ingredient Report # Regulations.gov | Name of New Dietary Ingredient | Firm | Date of Submission | Date of FDA's Response |
|---|---|---|---|---|---|
| 1 | Memo 2 | *Stevia rebaudiana* Bertoni (stevia or stevia leaf) | Sunrider International Inc | 7/7/1995 | 8/16/1995 |
| 2 | Memo 3 | Protoprotein nutraceutical Lab #PS-30 | Foodsmith Corporation | 7/10/1995 | 9/25/1995 |
| 3 | Rpt/NDI 1 | Theobromine | Tinos LLC | 1/22/1996 | 4/6/1996 |
| 4 | Rpt/NDI 2 | Tepozan (*Buddleja americana* L.) white sapote (*Casimiroa edulis*) | Malabar Productos Naturales S.A. De C.V | 2/7/1996 | 3/16/1996 |
| 5 | Rpt/NDI 3 | Lo Han Kuo Extract (fruit extract of Siraitia grosvenorii S.) (HerbaSwy™ Cucurbitaceae Fruit Extract) | HerbaSwy Labooratories, Inc. | 3/4/1996 | 4/17/1996 |
| 6 | Rpt/NDI 4 | Peptidase (enzyme derived from bacteria in the genus Serratia) (Serratiopeptidase™) | Specilalty Enzymes and Biochemicals Company | 5/17/1996 | 7/30/1996 |
| 7 | Rpt/NDI 5 | Bark extract of the Pao Pereira tree, Geissospermum vellosii (Pao V™) | Natural Source International, Ltd. Formerly called VIVA (USA) Inc. | 9/11/1996 | 11/13/1996 |
| 8 | Rpt/NDI 6 | Trigonella foenum-graeceum L. (Fenugreek) | Kentucky Biosafety Consultants Inc. | 9/17/1996 | 12/4/1996 |

**Figure 3-1 U.S. NDI Notification Data List**

Reference URL: https://www.fda.gov/media/160660/download?attachment

## 3.2 Understanding the FDA' s Response to an NDI Submission

Unlike a GRAS Notice, the FDA' s response to an NDI notification does not include a clear conclusion stating "FDA has no questions." Companies need carefully review the FDA' s response to understand the final outcome:

- **A "no objection" response is a procedural acknowledgment of receipt and typically includes the following standard procedural paragraphs:**

> *In accordance with 21 CFR 190.6(c),* ***FDA must acknowledge receipt of a notification for a new dietary ingredient.*** *For 75 days following the filing date, you must not introduce or deliver for introduction into interstate commerce any dietary supplement containing the new dietary ingredient that is the subject of this notification. Please note that acceptance of this notification for filing is a procedural matter and, therefore, does not constitute a finding by the FDA that the new dietary ingredient or the dietary supplement containing it is safe or not adulterated under 21 U.S.C. § 342. The FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredient if it is found to be unsafe, adulterated, or misbranded."*

Furthermore, the response letter does not contain the following negative statements: "does not comply with the requirements," "do not provide a sufficient basis/not a dietary ingredient," or "has significant concerns about."

# Chapter 4: NDI Submission Process and Requirements

## 4.1 NDI Submitter

Manufacturers or distributors of dietary supplements containing a new dietary ingredient, or manufacturers or distributors of the new dietary ingredient itself, must submit a notification to the FDA at least 75 days before the product is placed on the U.S. market.

## 4.2 NDI Notification Process

| Key Step | Description |
|---|---|
| Feasibility Assessment | Assess the feasibility and necessity of submitting an NDI Notification for the substance, and identify data gaps. |
| Pre-Submission Meeting with FDA (Optional) | Provide information to FDA, raise questions, and obtain preliminary feedback. |
| Dossier Preparation | Prepare a complete NDI Notification dossier in accordance with NDI notification requirements. |
| Submission | Submit the complete NDI dossier to FDA. |
| FDA files the notification | Upon receipt of the notification, FDA sends the notifier a confirmation letter stating the date of receipt and providing an NDIN number. That date marks the start of the 75-day premarket review period for the new dietary ingredient. |
| FDA Review | During the review period, FDA may raise questions and request additional information and materials. The types of FDA responses include:<br>• A no-objection acknowledgment letter;<br>• A determination that the dossier is incomplete under 21 CFR 190.6;<br>• An objection letter raising concerns about identity or safety information;<br>• A letter raising other regulatory issues regarding the ingredient or product. |
| Notifier Submits Additional Materials (if needed) | After the notifier submits additional materials, FDA may determine that the submission constitutes a major amendment and reset the 75-day notification period (21 CFR 190.6(d)). |
| Completion | FDA completes its review and issues a no-objection acknowledgment letter. After 90 days, the NDI Notification dossier and FDA's response letter (excluding confidential information) are made publicly available. |