Spoke

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New Dietary Ingredients (NDI)

In this Brief we share general background information on NDIs and New Dietary Ingredient Notifications

Technical Brief

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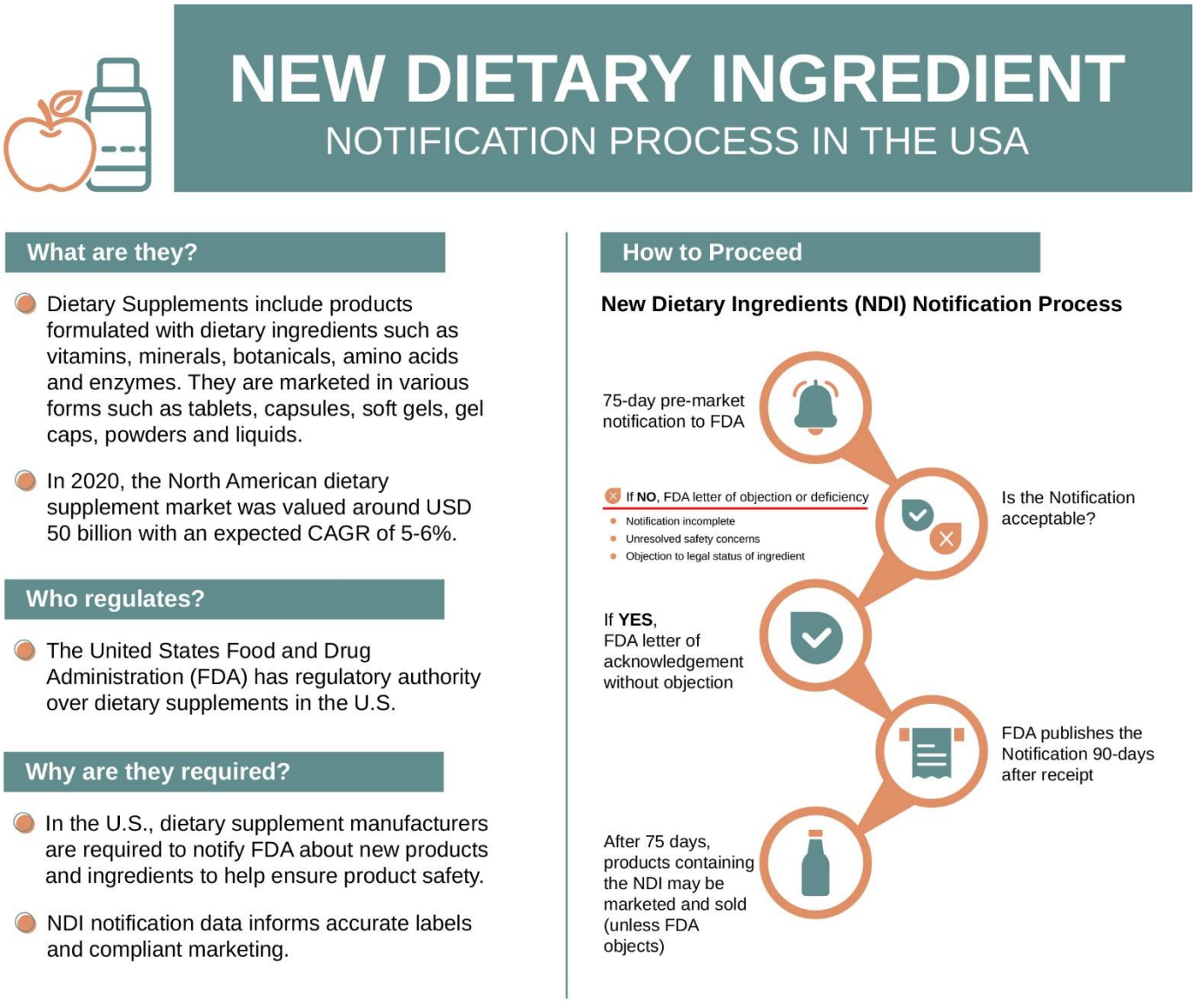
Introduction to NDI (New Dietary Ingredients)

Dietary supplements, the vitamin D softgel that you swallow for example, are comprised of dietary ingredients. This concept of "dietary ingredients" as the components of dietary supplements, and not food *per se*, was established by the Dietary Supplement Health and Education Act (DSHEA) of 1994. All ingredients used in dietary supplements prior to the passage of DSHEA were grandfathered as dietary ingredients, unless demonstrated to be unsafe. Such ingredients are often referred to as "old" dietary ingredients. DSHEA further established a procedure for new dietary ingredients (NDI) to be introduced. This process includes a New Dietary Ingredient Notification (NDIN) to the U.S. Food and Drug Administration (FDA) as depicted in Figure 1.

Fig. 1



This Technical Brief describes what a New Dietary Ingredient is and briefly touches upon how NDIs are related to two other pathways that can be used to bring an ingredient to market, food additives and GRAS ingredients. The Food

Additive Petition (FAP) and Generally Recognized As Safe (GRAS) pathways are similar to NDIN in that their primary purpose is to evaluate the safe use of an ingredient.

What is a Dietary Supplement?

As defined by DSHEA, a "dietary supplement" means:[1]

1. 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);

2. A product that -

   (A) Is intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form

   (B) If not in a form described in (A), is not represented for use as a conventional food or as a sole item of a meal or the diet; AND

   (C) Is labeled as a dietary supplement; **AND**

3. A product that –

   (A) does NOT include an article that has been authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public; **OR**

   (B) includes an article that has been authorized for investigation as described in (A), but was marketed as a dietary supplement prior to (A) occurring or if the Secretary of Health and Human Services (HHS), in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article is a lawful dietary ingredient despite (A).

Fig. 2: Definition of Dietary Ingredient

As defined by DSHEA, a "dietary ingredient" is:

(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 above.

Why are NDI important?

The New Dietary Ingredient Notification pathway allows the introduction of articles into dietary supplements that fall within the definition of a dietary ingredient (Fig. 2) but that were not used in dietary supplements prior to DSHEA, while evaluating safety before introduction. This differs

[1] 21 U.S.C. 321(ff) and 21 U.S.C. 350

from "old dietary ingredients" for which safe-use is presumed unless demonstrated otherwise by FDA.

Firms that produce ingredients for use in dietary supplements and/or produce finished dietary supplement products may pursue the NDIN pathway for a variety of reasons, but the following are three that are similar to why a firm may pursue a GRAS Notification:

Complying with Legal Mandate

Firms that produce dietary supplement products for the United States market, including those in liquid form, are required to only use ingredients that are legal for use in food or that are legal dietary ingredients. Doing otherwise creates an adulterated product that is subject to market removal and potential criminal charges.

For ingredients that do not have a history of use as articles used for food, the only way for an ingredient to be legally-incorporated into a dietary supplement is:

- Upon successful submission of a GRAS notification to FDA or the completion of a self-affirmed GRAS assessment (see Fig. 1)
- Upon successful submission of a new dietary ingredient notification (NDIN) to FDA

-OR-

- Upon regulatory change resulting from a Food Additive Petition (FAP)

Establishing safety

An integral part of any NDIN is the basic demonstration of acceptable risk (*cf.* safety) for the named substance and any impurities that might be present. This includes any byproducts that may be introduced by the manufacturing process.

Beyond the ethical and regulatory necessity of understanding the hazards of a product meant for human consumption, pursuing an NDIN helps protect a firm from product liability in the event that harm ensues. But more importantly, NDINs help to prevent the potential hazard in the first place. That is always good for business.

Avoiding drug preemption

Section 201(ff)(3)(B) of the FD&C Act disqualifies an ingredient from use in food or dietary supplement products if the ingredient is 1) an active ingredient in an approved drug or 2) if substantial clinical investigation of the substance as a drug has been conducted AND made public. In other words, if an article is first a drug, it is not a legal dietary ingredient and cannot be used in dietary supplements. This creates a race-to-market situation for articles used in dietary supplements versus articles used in drugs.

Importantly, it is FDA's position that "legal" marketing entails more than simple inclusion of the substance in marketed products—the substance must have been the subject of GRAS, food-additive, or new dietary ingredient notification (NDIN) pathways, if required, to be *legally* marketed.

How is an NDIN Accomplished?

In practice, the content and mechanics of NDINs are similar to those required for GRAS notifications to FDA with slightly different terminology, notification requirements and time horizons. The NDIN process is summarized in Figure 1., but a detailed treatment is available via FDA Draft Guidance Draft: New Dietary Ingredient Notifications and Related Issues.

Before proceeding with an NDIN, a firm should also be aware of what an NDIN accomplishes. An NDIN permits the article, or dietary ingredient, to be incorporated into dietary supplements, but not a food. This differs from GRAS Notifications, which can pertain to GRAS uses in both food and dietary supplements.

Other nuances exist between NDIN and GRAS that firms should be aware of before choosing the proper path. For example, whether ingredients are synthetically-produced or naturally-extracted may have a bearing on which pathway to pursue. FDA's current position is that an article produced through chemical synthesis—even if identical to a substance or molecule found naturally-occurring—makes the article ineligible for the NDIN pathway.

Conclusion

In the United States, any manufacturer of finished dietary supplement products is ultimately responsible for producing safe and legal products. One critical step in doing so is to deal only with suppliers that thoroughly understand and comply with Federal requirements such as NDIs and GMPs.

Spoke Sciences builds regulatory strategy and compliance into our solutions. We do not simply solve the solubility problem for your favorite ingredients, we also incorporate regulatory intelligence to up-level your compliance. Please contact us if you would like to learn more.