

Exceptions to the New Dietary Ingredient Notification Requirement: Utilizing GRAS as a Path Forward

A draft guidance for industry entitled “Dietary Supplements: New Dietary Ingredient Notifications and Related Issues” was issued by the Food and Drug Administration (FDA) in a Federal Register notice on July 5, 2011 (<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm>). This guidance provided detailed information about when and how to submit New Dietary Ingredient Notifications (NDINs) to the Agency. New Dietary Ingredients (NDIs) are typically intended for use in dietary supplements and, therefore, dialog ensued within the supplement industry. The extended comment period on this guidance recently ended on December 2, 2011, and numerous supplement- and consumer product-oriented organizations have submitted comments.

At a seminar sponsored by the United Natural Products Alliance (UNPA) in Salt Lake City on July 26-27, FDA’s Daniel Fabricant elucidated the intent of the guidance, stating: “Consumers should have access to dietary supplements that meet quality standards, that are free from contamination and are accurately labeled. FDA’s review of NDI

Notifications is an important preventive control mechanism to ensure that the consumer is not exposed to unnecessary public health risks in the form of new ingredients with unknown safety profiles.”

Pivotal to the interpretation of this draft guidance is a clear understanding of the criteria by which a product is defined as a dietary ingredient, under what conditions a dietary ingredient is considered to be new, and when a Notification

of the new dietary ingredient to FDA is necessary.

A dietary supplement is defined by Section 201 (21 U.S.C. 321) of the Federal Food, Drug and Cosmetic Act (FD&C Act) as 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).

Dietary supplements contain one or more dietary ingredients, which may or may not be considered “new,” according to the abovementioned FDA guidance document.

A dietary ingredient is an article used for food that falls into the categories defined above. A NDI is a dietary ingredient that was *not* marketed in the U.S. before October 15, 1994, and was present in the food supply as an article used for food, which either has

a history of use in conventional food. For example, if the NDI is an ingredient that is listed or affirmed by the FDA as Generally Recognized As Safe (GRAS), is self-affirmed as GRAS, or is approved as a direct food additive in the U.S., a Notification is not needed as long as the direct food additive of GRAS substance has been used in the food supply and is to be used as an NDI without chemical alteration. If the NDI were legally marketed in the

“FDA’s review of NDI Notifications is an important preventive control mechanism to ensure that the consumer is not exposed to unnecessary public health risks in the form of new ingredients with unknown safety profiles.” –Daniel Fabricant

or has not been chemically altered. Alternatively, a new dietary ingredient may be one that was not marketed in the U.S. before October 15, 1994, and it was *not* present in the food supply as an article used for food. Dietary ingredients that fall into these categories may need to be notified to FDA. It is important to note that FDA does not officially hold a list of “grandfathered” ingredients that were considered to be on the market prior to October 15, 1994, so companies may be required to provide documentation of an ingredient’s status.

There are exceptions to the Notification requirement for certain NDIs that have

U.S. as an ingredient for use in conventional food, it would qualify under section 413(a) (1) of the FD&C Act (21 U.S.C. 350b(a)(1)) as an ingredient exempt from the Notification requirements.

Two categories of ingredients that are conspicuously not included in the definition of dietary ingredients as stated in the FDA’s recent guidance are 1) synthetic compounds (even those that are chemically identical to their naturally occurring counterparts) and 2) probiotics derived from animal or human origin. Because these substances are not considered by FDA in the new guidance to be dietary

ingredients, they cannot be NDIs. These two categories of substances may be qualified for use in food via documentation of their GRAS status. Documentation of the GRAS status of a synthesized compound or probiotic of animal or human origin would also make these ingredients exempt from the Notification requirement.

Under sections 201(s) and 409 of the FD&C Act, and FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, the use of a food

a GRAS determination, which greatly enhances its transparency, is that the pivotal information must be publicly available in the published literature (Kruger et al., 2011).

In the case of a probiotic, a GRAS determination must document the safety of the specific strain of organism in the context of its intended use. The safety assessment includes consideration of potential vulnerability of the consumer or patient, dose and duration of consumption,

and thus it is critical to evaluate these parameters for each novel strain developed.

Regarding the GRAS evaluation of synthesized ingredients, there also are specific issues that must be considered. FDA has taken the position that a synthetic copy of a constituent of a botanical (source material) and thus cannot be a "constituent" of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FD&C

accounted for in the evaluation of the safety and GRAS status of the synthesized ingredient. To this end, GRAS can provide a pathway to market for such synthesized ingredients vs Notification as a New Dietary Ingredient.

Guidance on both the process and procedure for deciding when an NDI Notification is needed for a dietary ingredient (and how to submit an NDIN) is necessary, but there remain important issues to clarify at present, especially regarding what categories of substances may or may not qualify for consideration as a New Dietary Ingredient. Until these subtleties are addressed, industry can take comfort in the knowledge that the GRAS pathway may be an alternative pathway to market, while assuring consumers continued access to safe and useful products. **FT**

References cited in this column are available from the authors.

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The safety standard for GRAS substances is the same as that for a food additive petition, which is a "reasonable certainty of no harm."

substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food. General recognition of safety may be based on the views of experts qualified by scientific training and experience to evaluate the safety of substances that are directly or indirectly added to food. The safety standard for GRAS substances is the same as that for a food additive petition, which is a "reasonable certainty of no harm." Thus, in order to support the GRAS determination for a probiotic or a synthesized material, there must be the same quality and quantity of information available as would be sufficient to support a food additive petition. A unique feature of

and the form and frequency of administration. Probiotics are unique food ingredients in that they are live organisms when administered, and, unlike other food or drug ingredients, possess the potential for infectivity or *in situ* toxin production (Sanders, 2010). Specific issues such as potential pathogenicity and infectivity of a microbe intended to be used as a probiotic are considered; this includes an assessment of the ability of the organism to invade and translocate within a host, in addition to its ability to survive and multiply in the blood stream, produce toxins, assimilate and incorporate DNA into its genome, and acquire virulence genes and antimicrobial resistance. These factors may be specific to the strain of the probiotic,

Act (21 U.S.C. 321(ff)(1)(F)). Similarly, a synthetic version of a botanical (plant) extract is not an "extract" of a botanical under section 201(ff)(1)(F) because it was not actually extracted from the botanical. Although an ingredient may be synthesized to produce a copy of a botanical constituent, the chemical and toxicological equivalence of the synthetic version must be established, according to the current wording of the NDI guidance. From a practical point of view, a different matrix of trace-level impurities, by-products, and contaminants in the synthesized ingredient may differentiate it from the chemically identical compound that was isolated from a natural source. These contextual subtleties must be