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memorandum

TO Valued Dietary Supplement Clients **DATE** July 5, 2011

FROM Venable's FDA Practice Group

RE FDA Publishes Draft Guidance on New Dietary Ingredients ("NDIs")

On July 1, 2011, the U.S. Food and Drug Administration ("FDA") published its long-awaited Draft Guidance on New Dietary Ingredient ("NDI") notifications ("Draft Guidance"). The Draft Guidance can be found on FDA's website at http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm. The notice of availability of the Draft Guidance was published in the Federal Register on July 5, 2011. While comments on the guidance may be submitted to the agency at any time, to ensure consideration by the agency, comments should be submitted by October 3, 2011.

The positions articulated by FDA in the Draft Guidance can be expected to have a significant impact on all those who manufacture or distribute dietary supplement products. The Draft Guidance must be evaluated very carefully to determine the effects it may have on your company. Even those companies that previously submitted NDI notifications that were filed without comment should evaluate whether the use of the NDI is consistent with the four corners of the notification, including the dietary supplement formulation as stated in the original submission.

Please note that the Draft Guidance is a fairly long document, and we did not rehash every issue in this client alert. Rather, the purpose of this client alert is to point out nuances that may have an impact on your company. However, we are happy to discuss with you other issues that are not explicitly discussed below.

A. Background

By way of background, the federal Food, Drug, and Cosmetic Act ("FDCA") defines a "new dietary ingredient" as a dietary ingredient that was not marketed in the U.S. prior to October 15, 1994.[1] The statute defines a "dietary ingredient" as a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the

[1] 21 U.S.C. § 350b(c).

total dietary intake; or a concentrate, metabolite, constituent, extract, or combination" of any of the above.[2]

Importantly, the FDCA requires manufacturers or distributors of an NDI or dietary supplement that contains an NDI to submit a premarket notification to FDA at least 75 days before introducing the supplement into interstate commerce, unless the NDI and any other dietary ingredients in the supplement "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."[3] When an NDI notification is required, it must include a history of use or other evidence of safety for the ingredient. Based on that information, FDA determines whether it will file the notification with no questions asked, respond to the submitter with questions, or refuse to file the notification at all. However, until now, FDA has provided little guidance as to (1) what it considers "present in the food supply" to mean or (2) what type and quantity of evidence is sufficient to demonstrate safety such that the agency will permit the notification to be filed.

B. Important Takeaways from the Draft Guidance

The Draft Guidance contains the following important information:

- **Definition of "Marketing."** The Draft Guidance provides a definition of what the agency considers "marketing" for the purposes of establishing that a dietary ingredient was marketed in the U.S. prior to October 15, 1994 (*i.e.*, is a "grandfathered dietary ingredient"). In particular, the agency defines "marketing" as "selling or offering the dietary ingredient for sale (1) as a dietary supplement, (2) in bulk as a dietary ingredient for use in dietary supplements, or (3) as an ingredient in a blend or formulation of dietary ingredients for use in dietary supplements." The agency clarified that a dietary ingredient may be "marketed" by physically offering the article for sale at retail store, offering it for sale in a catalog or price list, or through advertising or other promotion, if the promotion makes it clear it is available for purchase. "Coming soon" advertisements do not qualify as marketing.

- **Evidence of Marketing.** The Draft Guidance also clarifies what type of documentation the agency would expect in order to demonstrate that a dietary ingredient was marketed in the U.S. prior to October 15, 1994 (*i.e.*, was a grandfathered dietary ingredient). Specifically, the agency indicates that it expects "written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994." The agency lists the following as examples of adequate evidence of marketing: sales records, manufacturing records, commercial invoices, magazine advertisements, mail order catalogues, or sales brochures. Consistent with the agency's response to the pyridoxamine citizen petition in 2009,[4] the Draft Guidance states that affidavits that are

[2] 21 U.S.C. § 321(ff)(1).
[3] 21 U.S.C. § 350b(a)(1).
[4] Letter from Michael A. Chappell, Acting Associate Commissioner for Regulatory Affairs, to Kathleen M. Sanzo, Esq., January 12, 2009, at 12 (FDA Docket No. 2005-P-0259).

unsupported by contemporaneously-created written records are not adequate to show that an ingredient was marketed prior to October 15, 1994.

  - **Industry Lists of "Grandfathered" Dietary Ingredients.** Consistent with the agency's previously-articulated position, the fact that an ingredient appears on one of the industry-complied lists of dietary ingredients that were marketed prior to October 15, 1994 (*i.e.*, lists of "grandfathered" dietary ingredients) is insufficient evidence that an ingredient is not an NDI.

- **Changes in Manufacturing Processes.** In the Draft Guidance, the agency states that even for a dietary ingredient that was marketed prior to October 15, 1994, if changes in the manufacturing process since that time have altered the chemical composition or structure of the ingredient, an NDI notification is likely required. The agency gives the following examples of changes to manufacturing processes that would necessitate an NDI notification: (1) an extract of a grandfathered dietary ingredient that is prepared using a solvent (because the final extract contains only a fractionated subset of the constituent substances in the original grandfathered dietary ingredient), (2) using a different part of the plant, or (3) a change producing nano-sized particles[5].

- **Use in Food.** An NDI notification need not be submitted for NDIs that have been present in the food supply as articles used for food, in a form in which the foods have not been chemically altered.
  - FDA interprets "food supply" as including the world food supply, not just that of the U.S.
  - The Draft Guidance details what the agency views as chemical alteration of an article previously used for food, which would trigger the notification requirement:
    - Dehydration, lyophilization, milling, and formation of a tincture of solution in water, a slurry, a powder, or a solid in suspension *do not* chemically alter an ingredient.
    - Any process that makes or breaks chemical bonds is considered chemical alteration. For example:
      1. Hydrolysis or esterification, unless the bonds created by the process are reversed when the ingredient is dissolved in water or during ingestion;
      2. Removal of some of the components of a tincture or solution in water;
      3. Use of solvents other than water or aqueous ethanol to make an extract;

[5] FDA notes the lack of safety evidence regarding nanomaterials in dietary supplements and recommends that notifiers contact FDA prior to submitting a NDI notification for an NDI that involves the application of nanotechnology.

4. High-temperature baking or cooking of a previously uncooked ingredient;
5. Changing the manufacturing method such that the chemical composition is significantly different (see above);
6. Changing agricultural or fermentation techniques to alter the chemical composition;
7. Fermentation using a different fermentation medium from the one used to make conventional foods in the food supply; or
8. Use of a botanical ingredient that is at a different life stage than previously used, such as making an extract from unripe rather than ripe apples.

- **NDI Submission is Supplement-Specific, Not Ingredient Specific.** Each NDI notification must contain information about the dietary supplement in which the new dietary ingredient will be used, including dosage and recommended uses, as well as other ingredients that will be included in the supplement. Because FDA relies on this supplement-specific information in making its determination about ingredient safety, the agency views each NDI submission as supplement-specific, rather than ingredient-specific. This is extremely important because the agency will require a new NDI notification for each specific formulation for which you use the NDI unless you meet all of the following requirements:
  (1) The daily intake level recommended or suggested in the labeling of the new supplement will be equal to or less than that specified in your prior NDI notification;
  (2) The new supplement does not have other dietary ingredients that were not included in or original NDI notification;
  (3) The target populations are the same or a subset of the target populations specified in your original notification;
  (4) All other conditions of use are the same as or more restrictive than the conditions of use described in your prior NDI notification; and
  (5) FDA did not express safety or other concerns in response to your prior NDI notification.

  - **Evaluation of Dietary Ingredients Other Than the NDI.** Because the agency will be evaluating the safety of the dietary supplement as a whole, FDA will require that the notification include the No-Observed-Adverse-Effect Level ("NOAEL") and Acceptable Daily Intake ("ADI") for *each* dietary ingredient, describe the toxicity data or adverse events that were the basis for determining the NOAEL, state the basis for the margin of safety for each ingredient, and discuss whether there is any possible synergy or interaction among any or all ingredients that could affect the safety of the dietary supplement. The notification must concisely evaluate known safety concerns and describe how the notifier concluded that the combination of ingredients can reasonably be expected to be safe.

- **Evaluation of Non-Dietary Ingredients.** Because the agency will be evaluating the safety of the dietary supplement as a whole, FDA will require that the notification include a description of the function of each ingredient that is not a dietary ingredient (*i.e.,* each food additive, color additive, and substance that is Generally Recognized As Safe ("GRAS")), including the technical effect and the quantity needed to achieve that technical effect. FDA also recommends inclusion of references to the applicable food additive, color additive, or GRAS determination.

- **Synthetic and Semi-Synthetic Versions of Extracts or Herbs are Not Dietary Ingredients.** The Draft Guidance states that synthetic or semi-synthetic versions of substances that are found in botanicals do not qualify as a "botanical" (or extract or constituent thereof) within the definition of a dietary ingredient found in 21 U.S.C. § 321(ff)(1). According to FDA, for example, use of a large amount of a strong oxidizing acid like sulfuric acid to process a botanical mixture may create a new "semi-synthetic" mixture that is no longer a mixture of components that were present in the original plant, and the mixture is no longer a dietary ingredient. This position is consistent with the agency's recent response to a citizen petition from OVOS Natural Health, Inc. requesting permission to use homotaurine as a dietary ingredient in dietary supplements.[6] In that response, FDA indicated that, although homotaurine occurs naturally in some plants, OVOS's homotaurine was not a botanical (or extract thereof) because it was made synthetically (*i.e.*, it was not extracted from any botanical).

- **Definition of "Amino Acid."** The Draft Guidance defines an amino acid as "an alpha-amino carboxylic acid used as a constituent of proteins or peptides." This is important for what it does not include. Importantly, based on this definition, if a substance is neither an alpha-amino carboxylic acid nor a constituent of proteins or peptides, then it is not an amino acid within the definition of a dietary ingredient and cannot be included in a dietary supplement unless it falls under one of the other categories of substances that qualify as dietary ingredients under 21 U.S.C. 321(ff)(1). This narrow interpretation of the definition of an "amino acid" likely excludes GABA (gamma-amino butyric acid), an ingredient that many dietary supplement companies use in their products. This position is also consistent with the FDA's recent decision on the OVOS citizen petition.[7]

- **Probiotics.** The Draft Guidance states that while certain microbial ingredients may be new dietary ingredients subject to the NDI notification requirement, others may not be dietary ingredients at all. Specifically, the agency is unlikely to view microorganisms that have never been consumed as food as dietary ingredients. This is because probiotics are generally not vitamins; minerals; herbs or other botanicals; amino acids;

[6] FDA/CFSAN Response to OVOS Natural Health, Inc.- Petition Denial, Docket ID: FDA-2009-P-0298 (Feb. 23, 2011).
[7] *Id*.

or concentrates, metabolites, constituents, extracts, or combinations thereof. Thus, the only way that a probiotic can meet the definition of a dietary ingredient is if it is a dietary substance for use by man to supplement the diet by increasing the total dietary intake. FDA has interpreted that to mean that the ingredient was an intentional constituent of food. Thus, bacteria that are used to produce fermented foods and are eaten without cooking or pasteurization may meet the definition of a dietary ingredient. However, others may not be dietary ingredients. The Draft Guidance also provides information on the content of notifications for ingredients produced using fermentation.

  - **Pathogens**. FDA indicated that it does not view pathogenic species of bacteria as dietary ingredients--even though they may have been present in food as contaminants. In addition, the NDI notification for any microbial NDI should identify any human pathogens that are phylogenetically related to the microbial NDI at the species or genus level and should identify any toxins known to be present in the same species or in a phylogenetically related family or genus. The NDI notification should also document the absence (or the amount, if present) of such toxins in the NDI.

  - **Antimicrobial Resistance.** The agency has indicated that if a microbial NDI is resistant to any clinically-relevant antibiotics, the NDI notification should also include an assessment of the ability of the antibiotic resistance genes to mobilize and transfer to human pathogens under the conditions of use of the dietary supplement.

  - **Pigs as Animal Model for Digestive Tract.** If history of use data are inadequate to support the safety of a microbial NDI, studies in humans or animal models should be included. FDA states that it considers pigs to be the most appropriate animal model for the human digestive tract.

- **Ester Ingredients.** The Draft Guidance indicates that the safety of an ester ingredient in an NDI notification can be inferred if you can provide data to demonstrate that the ingredient is rapidly hydrolyzed in the stomach or intestine into an acid and an alcohol, and that the acid and alcohol each have a long history of safe use in food.

- **Comprehensive Safety Profile and Safety Narrative.** The Draft Guidance describes two new sections that should be included in every NDI notification: the Comprehensive Safety Profile and the Safety Narrative. The Comprehensive Safety Profile should provide objective summaries of all available human and animal toxicological information and should substantiate the safe use of the NDI in humans under the proposed conditions of use described in the notification. The Safety Narrative should include a concise summary of the scientific basis for your conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe when used under the conditions recommended or suggested in the supplement's labeling. It should explain how the various pieces of data and information fit together to form the basis for

your conclusions about the safety of the dietary supplement. The Draft Guidance provides detailed information as to what the agency expects in these two sections.

- **Thorough Description of Types of Evidence The Agency Will Likely Require.** The Draft Guidance provides a thorough description of the types of evidence that the agency will likely expect depending on the intended frequency and duration of use of the supplement, the intended intake levels, and whether the NDI has a documented history of safe use. Table 2 sets out the information in chart form.

    - **Twenty-Five-Year Minimum for History of Safe Use.** The agency specified that it considers 25 years of widespread use to be the minimum required to establish a history of safe use (without additional safety data).

    - **One-Year Or Two-Year Studies Likely Required If No History of Safe Use.** If there is no history of safe use for an NDI, and if the proposed use is either intermittent or daily chronic, among many other requirements, the agency has indicated that it expects either a one-year chronic toxicity study or a two-year carcinogenesis study in at least two animal species.

    - **Human Studies May Be Required.** The Draft Guidance acknowledges that human studies are not explicitly required by statute, but at the same time states that there may be circumstances in which it is required to conclude that an ingredient is reasonably expected to be safe under the proposed conditions of use.

    - **Highest Dose To Be Used in Animal and Human Safety Studies.** Highest dose in animal studies should be the maximum tolerated dose ("MTD"), which is the dose that causes no more than a 10% reduction in body weight and does not produce mortality, clinical signs of toxicity, or pathologic lesions. Typically this is determined by a 14-day range-finding oral study in an appropriate animal model. The highest dose in human studies should be governed by safety considerations, but should be as high as feasible and at least as high as the total daily intake level of the NDI under conditions of use proposed in the notification—preferably higher. The Draft Guidance references several sources of testing protocols.

- **Flow Chart for Determining When to Submit an NDI Notification.** The agency has provided a flow chart for companies to use in determining whether to submit an NDI notification. The flow chart can be found at Appendix A to the Draft Guidance.

- **New NDI Notification Form.** The agency has provided a new NDI notification form that may be used but is not mandatory. The form can be found at Appendix B to the Draft Guidance.

C. Next Steps

We urge all companies that manufacture or private label distribute dietary supplement products to engage in a thorough evaluation of each of their products to (1) confirm that all ingredients in the product qualify as dietary ingredients and (2) determine whether an NDI notification is necessary for that product. Even those companies that previously submitted NDI notifications that were filed without comment should evaluate whether the use of the NDI is consistent with the four corners of the notification, including the dietary supplement formulation as stated in the original submission.

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Please feel free to contact Claudia Lewis (202.344.4359/ calewis-eng@venable.com), Todd Harrison (202.344.4724/ taharrison@venable.com), or Michelle Jackson (202.344.4492/ mcjackson@venable.com) with any questions you might have or for assistance in (1) filing comments with FDA, (2) evaluating your current products, or (3) preparing NDI notifications to be filed with FDA.