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New Dietary Ingredient Notification Procedures and Timeframes

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According to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 350b(a)(2)), manufacturer or distributor of a new dietary ingredient (NDI) which has not been present in food supply as an article used for food, or of a dietary supplement containing NDI, must submit a premarket safety notification to FDA at least 75 days before introducing product into interstate commerce. According to section 201(ff) (1) of the FD&C Act (21 U.S.C. 321(ff) (1)), a "dietary ingredient" is any one of the following:

- A vitamin;
- A mineral;
- An herb or other botanical;
- An amino acid;
- A dietary substance for use by man to supplement diet by increasing total dietary intake; or
- A concentrate, metabolite, constituent, extract, or combination of any dietary ingredient from preceding categories.

The manufacturer or distributor must include following information in its premarket NDIN:

- Name and complete address of manufacturer or distributor that is submitting notification.
- Name of NDI that is subject of premarket notification. For botanicals, Latin binomial name must be given, including author citation (i.e., name of scientist who gave botanical its Latin binomial name).
- A description of dietary supplement (or dietary supplements) that contains NDI, including:
  - Level of NDI in dietary supplement; and
  - Conditions of use recommended or suggested in labeling of dietary supplement, or if no conditions of use are recommended or suggested in supplement's labeling, ordinary conditions of use of supplement.
- History of use or other evidence of safety establishing that dietary ingredient, when used under the conditions recommended or suggested in labeling of dietary supplement, will reasonably be expected to be safe.
- Signature of a person authorized by manufacturer or distributor to sign notification on its behalf.

NDIN Procedures

The manufacturer or distributor of a dietary supplement that contains an NDI, or manufacturer or distributor of NDI, must notify FDA. Although FDA does review NDINs from manufacturers and distributors of NDIs, notifications from ingredient manufacturers do not eliminate requirement for a NDIN from manufacturer or distributor of dietary supplement in which NDI will be used unless prior notification for NDI included information about dietary supplement, specifically:

- A description of dietary supplement that contains information required by 21 CFR 190.6(b)(3); and
- History of use or other evidence of safety that formed basis of the notifier's conclusion that dietary supplement would reasonably be expected to be safe under its labeled conditions of use.

For NDINs that cover multiple dietary supplements and include safety data for a range of doses, daily intake levels, or other variations in conditions of use, safety data must be submitted up to and including highest dose and daily intake level at which NDI may be marketed, indicate any lower daily intake levels at which NDI may be marketed, and include research that evaluates statistically relevant data points, such as a range of daily intake levels, to strengthen safety analysis.

NDIN should be well organized to facilitate an efficient and timely FDA review. If NDIN is filed electronically, system organizes NDIN. FDA encourage electronic submission to help ensure that a complete NDIN is submitted and to enhance FDA's ability to process and review NDIN efficiently Instead of electronic submission, a paper NDIN may also be submitted. FDA recommend that paper NDIN be organized by sections, with continuous and consecutive pagination throughout notification. page number should appear in same location on every page. In addition, each subject area should begin with a new page to facilitate division of NDIN among reviewers. FDA encourages those who wish to submit NDINs on paper to consult a recommended template for organizing a paper NDIN.

Information in NDIN

NDIN should:

- Specify which of the dietary ingredient categories NDI belongs to and explain basis for conclusion;
- Describe manufacturing process used to make NDI, including process controls;
- Describe physical properties and chemical or molecular composition and structure of NDI;
- Include a specification sheet (preferably in table form) that describes critical identity and safety attributes of NDI, including purity and strength of NDI and identities and levels of any impurities and contaminants.

NDIs should be described in a way that accurately communicates their basic nature and characterizing ingredients or components, as appropriate. If NDI was subject of a previous NDIN submitted by applicant or supplier (manufacturer or distributor from which NDI is obtained), NDIN number should be included.

NDIN should contain a description of dietary supplement in which NDI will be used, including:

- Level of NDI in dietary supplement per serving;
- Identity and level of any other dietary ingredients and non-dietary ingredients (e.g., binders and fillers) in dietary supplement per serving;
- A description of manufacturing process of dietary supplement, including process controls;
- A specification sheet for dietary supplement that describes its critical safety attributes; and
- Conditions of use recommended or suggested in labeling of dietary supplement, or if no conditions of use are recommended or suggested in labeling of dietary supplement, a discussion of ordinary conditions of use of dietary supplement. conditions of use include serving form (e.g., tablet, capsule, powder, liquid), serving size (e.g., weight or volumetric measure per serving), frequency of use (e.g., number of servings per day and interval between servings), duration of use, instructions for use, target population, excluded populations (if any), and any other restrictions on use.

NDIN should contain only data or information that identifies NDI or dietary supplement containing NDI, or that helps provide a basis for safety of NDI or dietary supplement. An NDIN should not contain general or extraneous information. An NDIN should not include published review articles about other products, or publications and websites that promote other products, unless information in articles or websites can be specifically linked to NDI or dietary supplement that is subject of notification. An NDIN also should not include data or information intended to satisfy other regulatory requirements.

Submission of NDIN

NDIN can be submitted electronically through FDA's CFSAN Online Submission Module (COSM). COSM's data validation helps prevent incomplete notifications by ensuring that all required fields are completed before NDIN is

submitted. Firms that prefer to submit a paper NDINs still have option to do so. If NDIN is submitted on paper, original copy and two copies of NDIN should be submitted. If NDIN is submitted through COSM, no need to submit any duplicate.

Electronic submission can be done via COSM at https://cfsanonlinesubmissions.fda.gov.

Paper NDIN should be sent to:

Office of Dietary Supplement Programs (HFS-810)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740-3835

For electronic submission, COSM provides instructions for listing references. For paper NDINs, FDA recommend listing references in a reference section at end of notification. list of references for both paper and electronic NDINs should include full citations to all published and unpublished sources cited or relied upon in notification. Furthermore, list of references should include reference number or short descriptor used to cite to each study or publication in the body of NDIN.

Whether submitting electronically or on paper, all references to published information offered in support of NDIN must be accompanied by reprints or photocopies of such references. That means submitting a photocopy or reprint of full text of each reference. Submitting only abstract or bibliographic citation of a publication is not sufficient for FDA to evaluate whether study supports assertions in your NDIN. In addition, FDA do not recommend submitting abstracts that are only published report of a scholarly or scientific work. Because abstracts do not contain sufficient information to judge reliability of scientific conclusions drawn in study and generally do not undergo rigorous review and editing used to evaluate full-length publications, they do not provide data that are useful in evaluating safety of an NDI.

Material written in a foreign language may be used as part of basis for a conclusion that NDI will reasonably be expected to be safe under conditions of its intended use in dietary supplement; however, material must be accompanied by an accurate and complete English translation.

During review of NDIN, FDA may request submission of raw data or other additional information. If additional information is a substantive amendment, FDA will reset filing date and start a new 75-day review period. NDIN should be signed by person designated by manufacturer or distributor of dietary supplement that contains NDI. This person should be primary contact, who represents notifier in any discussions with FDA about NDIN and who designates any additional contact persons in notification or in subsequent correspondence. For paper submissions, typed or printed name, title, address, telephone number and, if available, email address of primary contact person should be listed at end of the cover letter that accompanies notification so that FDA can reach them when necessary. Typed or printed names, titles, addresses, telephone numbers and, if available, email addresses of additional contact persons for NDIN should be listed after contact information for primary contact.

Review of NDIN

Date when FDA receives a complete NDIN is the date of that notification's filing. A complete NDIN is a notification that contains all information required by 21 CFR 190.6. The date of filing is start of 75-day premarket review period during which manufacturer or distributor of a dietary supplement containing an NDI may not market dietary supplement.

An incomplete NDIN is one that does not contain all information required by 21 CFR 190.6. If NDIN is incomplete, FDA will inform via COSM or in writing by U.S. mail or a courier service. FDA does not evaluate safety or identity information in incomplete NDINs. Examples of omissions that can cause an NDIN to be incomplete include:

- Material in a language other than English that is either not translated or is translated inaccurately or incompletely.
- Citations to published literature for which a full copy of publication is not provided.
- An NDIN that is not signed, or contact information that is inaccurate and does not permit FDA to establish contact with notifier.
- Failure to provide the Latin binomial name, including author citation, for any ingredient that is a botanical or derived from a botanical.

After reviewing a submission of additional information, FDA may determine that submission is a substantive amendment and reset filing date. After receiving an NDIN, FDA sends an acknowledgement of receipt to notifier stating date of receipt of notification and provides NDIN number assigned to the notification. The date of NDIN's receipt is also filing date on which 75-day prohibition on introducing NDI-containing dietary supplement into interstate commerce begins. FDA may use electronic communication to send acknowledgement of receipt. In this communication, FDA will also state that we intend to send a detailed response letter within 75 days of filing date.

After finishing review, FDA will send response letter to the notifier.

Examples of types of response sent by FDA include:

- Letter of acknowledgement without objection;
- Letter listing deficiencies that make NDIN incomplete under 21 CFR 190.6;
- Objection letter raising concerns with adequacy of the identity information or safety information
- Letter raising other regulatory issues with ingredient or product

Receiving an acknowledgement letter without objection means that FDA's review of NDIN did not find any reason to object to notifier's basis for concluding that NDI and dietary supplement containing NDI will reasonably be expected to be safe. However, such a letter does not constitute an independent finding by FDA that NDI and the dietary supplement that contains NDI are safe, or that they are not adulterated under section 402(f) of FD&C Act. NDIN response letter sent at end of FDA's review will be kept confidential for 90 days after filing date. After 90-day date, NDIN response letter will be placed on public display at www.regulations.gov, except for any information that is trade secret or CCI. Any information in notification that is trade secret or CCI should be identified either by marking information where it appears in notification or by identifying this information in a separate document that accompanies NDIN and that is explained basis for this belief. If there are no trade secrets or CCI contained in NDIN, they should be stated this in the notification.

Some firms request meetings with FDA to ask questions and get preliminary and non-binding feedback from FDA regarding planned or potential NDINs. It is entirely voluntary to request feedback on a potential or planned NDIN by sending email to FDA at NDITEAM@fda.hhs.gov, using subject line "[Firm Name]– Pre-NDIN Meeting Request."

Recommended Template for Organizing an NDIN that is Submitted on Paper

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