New Dietary Ingredient Notification Master Files for Dietary Supplements: Guidance for Industry

Draft Guidance

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Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that FDA considers your comment on this draft guidance before we begin work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2024-D-0706 listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact the Food and Drug Administration, Office of Dietary Supplement Programs, 5001 Campus Drive (HFS-810), College Park, MD 20740, Toll Free 855-543-3784, or 240-402-2375.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

April 2024

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance at the phone number listed on the title page.

I. Introduction

This guidance provides recommendations to industry on Master Files for new dietary ingredient notifications (NDINs).[2] For purposes of this guidance, a new dietary ingredient notification master file (NDIN Master File or Master File) is a file containing identity, manufacturing, and/or safety information relating to a new dietary ingredient (NDI) that the Master File owner submits to FDA for use in evaluating a potential future NDIN by the Master File owner or by another person designated by the owner (e.g., business partner, supplement manufacturer).[3] A Master File contains information about an NDI, a dietary supplement containing an NDI, or both. The Master File owner may refer to the Master File in an NDIN or may grant written authorization to other parties to incorporate information from the Master File by reference in NDINs. A written authorization granting a right of reference to a Master File in an NDIN does not include the right to see or copy the Master File.

The recommendations in this guidance expand upon and replace the recommendations related to Master Files in FDA's revised draft guidance, *Dietary Supplements: New Dietary Ingredient*

[1] This guidance has been prepared by the Office of Dietary Supplement Programs (ODSP) and the Office of Regulations and Policy in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration (FDA).

[2] A new dietary ingredient (NDI) is a dietary ingredient that was not marketed in the U.S. before October 15, 1994 (21 U.S.C. 350b(d)). Under section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the manufacturer or distributor of an NDI, or of the dietary supplement that contains the NDI, must submit a premarket notification to FDA at least 75 days before introducing the product into interstate commerce or delivering it for introduction into interstate commerce, unless the NDI and any other dietary ingredients in the dietary 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" (21 U.S.C. 350b(a)(1)). An NDIN must contain the information, including any citation to published articles, that provides the basis on which the manufacturer or distributor of the NDI or dietary supplement (the notifier) has concluded that the dietary supplement containing the NDI will reasonably be expected to be safe (21 U.S.C. 350b(a)(2)).

[3] In this guidance, the word "person" includes business entities and other organizations in addition to individuals.

Notifications and Related Issues (the 2016 revised draft guidance). Our recommendations reflect input received from the public and industry in response to the 2016 revised draft guidance. They also reflect FDA's discussions with stakeholders.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

Under section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 350b(a)(2)), the manufacturer or distributor of an NDI that has not been present in the food supply as an article used for food, or the manufacturer or distributor of a dietary supplement containing such an NDI, must submit an NDIN to FDA at least 75 days before introducing the product into interstate commerce. The NDIN must contain the information, including any citation to published articles, which provides the basis on which the manufacturer or distributor of the NDI or dietary supplement (the notifier) has concluded that the dietary supplement containing the NDI will reasonably be expected to be safe (21 U.S.C. 350b(a)(2)).

FDA hopes that, by describing how to submit and use Master Files, this guidance will help the industry to more easily comply with the requirement to submit NDINs. Accordingly, this guidance provides recommendations on how to establish, update, and close a Master File, as well as recommendations regarding how a Master File owner can authorize other parties to reference the Master File in an NDIN.

III. Discussion

A. How to Establish a New Dietary Ingredient Notification Master File

1. *What is an NDIN Master File?* An NDIN Master File or Master File is a file containing identity, manufacturing, and/or safety information relating to an NDI that the Master File owner submits to FDA for use in evaluating a potential future NDIN by the Master File owner or by another person designated by the Master File owner (e.g., business partner, supplement manufacturer). An NDIN Master File contains information about an NDI, a dietary supplement containing an NDI, or both. Master Files benefit NDIN submitters with a right of reference by allowing them to refer to data already on file with FDA, instead of having to develop the data themselves and resubmit it in each NDIN for the same ingredient.

[4] See, e.g., Public Meeting to Discuss Responsible Innovation in Dietary Supplements (May 16, 2019). Meeting transcript available at: https://www.fda.gov/food/workshops-meetings-webinars-food-and-dietary-supplements/public-meeting-discuss-responsible-innovation-dietary-supplements.

2. *What to submit*. To establish an NDIN Master File, FDA recommends that the following information be submitted to FDA electronically through the Center for Food Safety and Applied Nutrition (CFSAN) Online Submission Module (COSM) or by mail.

- A cover letter that includes:
  - (i) A statement that the information is being submitted as an NDIN Master File;
  - (ii) A brief description of the content of the Master File;
  - (iii) The name, mailing address, email address, and phone number of the Master File owner (the person establishing the Master File);
    - a. If the Master File owner wishes to authorize a representative to grant a right of reference to the Master File on behalf of the Master File owner and communicate on behalf of the Master File owner, the name, mailing address, email address, and phone number of that authorized representative;
    - b. If the Master File owner or authorized representative does not reside in, or have a place of business in the United States, the name, mailing address, email address, and phone number of an authorized representative who resides in or has a place of business in the United States.
- A table of contents;
- The information that is to be made part of the Master File;
- A list of each person authorized to reference the Master File (including name, mailing address, email address, and phone number); and
- For each such person authorized to reference the Master File, any limitations on the authorization (e.g., whether the Master File owner is granting a right of reference to only certain sections of the Master File and, if so, which sections).

Submissions should be in English with pages numbered sequentially.

3. *Where to submit*. We recommend electronic submission to FDA via COSM.[5] COSM is a web-based tool that assists users in submitting fully electronic submissions to FDA.

If the NDIN Master File owner chooses not to submit the information electronically, it should be mailed to the following address:

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

[5] https://cfsan-onlinesubmissions.fda.gov/farmonline/#/login.

4. *Trade secrets and confidential commercial information (CCI)*. Although some or all of the data in an NDIN Master File may be trade secret information[6] or CCI[7] (and generally exempt from public disclosure), there is no presumption that any particular information in the Master File is trade secret information or CCI. A determination of whether specific data and information in an NDIN Master File is exempt from public disclosure is based on the status of the data and information under the Freedom of Information Act (FOIA) and FDA disclosure regulations at 21 CFR part 20, rather than on the type of file in which the data and information is stored. We recommend that the Master File owner clearly identify any information in the NDIN Master File that the Master File owner believes is trade secret or CCI—either by marking the information where it appears in the Master File or by identifying this information in a separate document that accompanies the NDIN Master File—and that the Master File owner explain the basis for this belief. Likewise, if the Master File owner believes there are no trade secrets or CCI contained in the NDIN Master File, we request that the Master File owner state this in the Master File.

FDA will include a list of NDIN Master Files that are referenced in published NDINs on its website and expects to update this list on a quarterly basis. This list will include the NDIN Master File Number, Submission Date, Subject, and Master File Owner.

B. How to Update or Close a New Dietary Ingredient Notification Master File

1. *Updates to a Master File*. If any information in the NDIN Master File changes, such as the parties the Master File owner authorizes to refer to the NDIN Master File in NDINs, the Master File owner should update the NDIN Master File (electronically through COSM or through paper submission to FDA) and notify the authorized parties of the changes.

2. *Closure of a Master File by the Master File owner*. If a Master File owner wishes to close the Master File, we recommend that the Master File owner notify the Office of Dietary Supplement Programs via email at NDITeam@fda.hhs.gov. However, if the Master File owner is unable to contact FDA via email, the Master File owner should send a notice to the mailing address provided above and specify the date the Master File should be closed. Additionally, FDA recommends that the Master File owner notify all parties currently authorized to reference the Master File of the closure. Once closed, the Master File will no longer be available for reference in future NDINs but will still be incorporated by reference into previously submitted NDINs.

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[6] A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort (21 CFR 20.61(a)). There must be a direct relationship between the trade secret and the productive process, such as information relating to the manufacturing process (see 21 CFR 20.61(a)).

[7] CCI covers information that is confidential and used in a business (21 CFR 20.61(b)). Examples of CCI might include sales statistics, dollar volume, amount, or source of income (e.g., a company's list of customers), profits or losses, expenditures (of any person, firm, partnership, corporation, or association), names of suppliers or subcontractors, or brand of equipment.

C. How Persons Authorized by the Master File Owner Can Use a New Dietary Ingredient Notification Master File

The Master File owner may grant written authorization to other parties to reference information from the NDIN Master File through a Letter of Authorization (see Appendix A). The ability to refer to data in an NDIN Master File can be helpful to persons that are preparing NDINs. However, a written authorization to reference a Master File in NDINs does not include the right to see the Master File unless the Master File specifies such access is authorized.

The Letter of Authorization should describe the specific sections of the NDIN Master File to which the Master File owner is authorizing a right of reference. Persons who have been granted written authorization to reference the NDIN Master File, or a portion thereof, may rely on the information in the Master File to support an NDIN without the Master File owner having to disclose this information to them. If there are any questions about the content of the NDIN Master File, the authorized person should discuss the questions with the Master File owner. Before using data from an NDIN Master File, the authorized person and the Master File owner should compare the conditions of use recommended in the NDIN Master File with those proposed in the NDIN. If the conditions of use in the NDIN do not match those in the NDIN Master File, the data in the NDIN Master File might not apply to the product evaluated in the NDIN.

If a party is not already listed in the NDIN Master File and the Master File owner wishes to grant use of the master file to such party, the Master File owner should submit the Letter of Authorization to FDA on the Master File owner's letterhead and send a copy of the Letter of Authorization to the authorized party. The authorized party should include a copy of the Letter of Authorization when referring to the NDIN Master File in their NDIN. If the authorization does not extend to the entire Master File, the Letter of Authorization should specify the part(s) of the NDIN Master File each authorized party is authorized to use.

D. FDA's Role in Reviewing and Administering New Dietary Ingredient Notification Master Files

1. *Review of an NDIN Master File*. FDA will conduct a substantive review of an NDIN Master File when we receive an NDIN that incorporates information from the NDIN Master File by reference. When FDA receives an NDIN that relies on information in an NDIN Master File to which the notifier has a right of reference, we will review the referenced information in the NDIN Master File as part of our standard review of the NDIN. FDA does not intend to conduct a scientific review of an NDIN Master File without a corresponding NDIN.

2. *Review of an NDIN incorporating an NDIN Master File by reference*. When FDA receives an NDIN that refers to information in an NDIN Master File to support the NDIN, we will first verify whether the Master File owner has given the notifier permission to incorporate the specified information from the NDIN Master File. After the authorization check, FDA will conduct a standard NDIN review, considering the information cited from the NDIN Master File as part of its review of whether there is evidence of safety establishing that the NDI, when used

under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.

If questions arise during the review of the NDIN, FDA will contact the notifier, except that if the questions relate to the content of the Master File, FDA will contact the Master File owner directly for clarification. If additional information not in the NDIN Master File is needed for FDA to complete its review of a notification, FDA will inform the notifier of the general subject of the information needed without disclosing specific details about the NDIN Master File content, and the notifier can either ask the Master File owner to supplement the NDIN Master File or otherwise provide the necessary information directly to FDA. Because notifiers are responsible for ensuring the completeness of their notifications, FDA does not intend to request information from the Master File owner on the notifier's behalf.

Appendix A: Model Letter of Authorization

[Master File owner's Letterhead]

[Date]

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

SUBJECT: MF NUMBER –Letter of Authorization for Company A

Dear FDA ODSP Staff:

Company B authorizes Company A to incorporate by reference information from our New Dietary Ingredient Notification Master File, MF NUMBER, into any new dietary ingredient notifications submitted by Company A. [*If the authorization covers only part of the master file, add:* This authorization covers only the following portions of the Master File: [*list sections or page numbers*]. [MF OWNER] also authorizes FDA to review this information in [MF NUMBER] when considering any notification filed by [AUTHORIZED PARTY].

Authorized Party Information

Authorized Party Name	**Contact(s)**	**Limitation(s) to Authorization**
Company A	[Name], [Title] [Address] [Phone number] [Email address] [Name], [Title] [Address] [Phone number] [Email address]	Authorized to reference only Sections X and Y *or* N/A [*if no limitations*]

Please let me know if you have any questions.

Sincerely,

Joe Johnson
Vice President, Company B

cc: Company A