New Dietary Ingredient Master File Framework

A Proposal Developed by CRN's Master File Working Group

I. Introduction

Under 21 U.S.C. §350b(d), a new dietary ingredient (NDI) is a dietary ingredient that was not marketed in the United States before October 15, 1994. If the marketer of an NDI determines that the NDI was not an article used for food in a form in which the food has not been chemically altered, then the marketer must submit to the Food and Drug Administration (FDA), at least 75 days before the NDI is introduced into interstate commerce, information that is the basis on which the marketer has concluded that a dietary supplement containing the NDI will reasonably be expected to be safe (21 U.S.C. §350b(a)). FDA reviews this information to determine whether it provides an adequate basis for such a conclusion.

To bring NDIs to market, ingredient manufacturers invest in the generation of safety data and development of manufacturing processes. With such significant investment, protection of intellectual property and technology would incentivize ingredient manufacturers to use the NDI notification process as well as to continue to research and develop NDIs to advance innovation. Toward this end, FDA can implement a master file system for NDIs. A master file is already a common submission to FDA for a drug ingredient or product, excipient, colorant, flavor or material used in their preparation. Introducing the master file as part of the NDI notification process will, in concept, help to protect ingredient manufacturers' investments in innovation. The master file owner, or holder, may authorize another entity to incorporate by reference information in its NDI master file in support of an NDI notification. Without authorization, one ingredient manufacturer cannot claim to have the same NDI as another. Further, FDA should not review NDI notifications that improperly references an NDI master file. With an NDI master file system, FDA and the supplement industry would be able to appreciate ingredient manufacturers' investments in developing NDIs.

This document provides a framework for the development of an NDI master file system, including master file contents, submission process, and authorization mechanisms to protect confidential information.

II. Purpose

An NDI master file is a submission to FDA by a person (the holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate master file information by reference when the holder submits an NDI notification under 21 CFR 190.6, or to permit the holder to authorize a third party to rely on the information to support an NDI notification to FDA without the holder having to disclose the information to the third party. An NDI master file is submitted solely at the discretion of the holder. FDA neither approves nor disapproves the submission to an NDI master file, and reviews master file information only in the context of an NDI notification under 21 CFR 190.6. An NDI master file may contain specific confidential

information included in a submission to the agency, such as information about the manufacturing, processing, and human and animal safety data related to the NDI.

III. Submissions to an NDI master file

Each NDI master file submission should contain a cover letter, administrative information about the submission, and technical information pertaining to the NDI (see Annex II for details). The holder should clearly identify any information that is considered trade secret or confidential. The holder also determines the level of detail included in the NDI master file.

NDI master file holders may appoint an agent who is familiar with FDA regulations, guidances, and procedures. However, NDI master file holders, not their agents, are responsible for the contents of their NDI master files. Holders should list the types of NDI master file information that agents can submit on their behalf in agent letters of appointment. The holder should submit any agent appointment letter(s) to FDA as part of the NDI master file's administrative information.

IV. Review of an NDI master file

Administrative review: FDA will examine an original NDI master file submission upon receipt to determine if it meets the requirements for format and content. This initial administrative review is not an evaluation of whether an NDI master file is sufficient to support an NDI notification. FDA only assesses whether the submission contains all required elements in order to assign an NDI master file number. If the submission is complete, FDA will acknowledge its receipt and assigns it an NDI master file number. This number can be used by the holder to identify the master file in letters of authorization (LOAs) and referenced by an authorized third party when incorporating information in the NDI master file to support an NDI notification. If a submission is not complete, FDA will not assign an NDI master file number and will provide the holder with a letter explaining why the submission was not accepted.

FDA does not approve or disapprove an NDI master file. FDA performs a complete review of the technical information in an NDI master file only when an authorized party submits an NDI notification referencing the NDI master file.

V. Authorization to reference an NDI master file

Once the NDI master file holder submits the master file and obtains an NDI master file number from FDA, the holder may authorize any person, including itself, to reference the NDI master file by submitting an LOA for each authorized party. An LOA should be submitted even if the authorized party and the holder are the same person. The NDI master file holder should send a copy of the LOA to FDA and a copy of the LOA to the authorized party. The authorized party should include a copy of the LOA with its NDI notification. The LOA permits FDA to access the NDI master file information in support of its review of an NDI notification submitted by the party identified in the LOA.

The letter of authorization should include:

- NDI master file number
- Name of NDI master file holder
- Name of person(s) authorized to incorporate information in the master file by reference
- Specific information referenced by the LOA, including section numbers and page numbers
- Statement of commitment affirming that the NDI master file is current; that the holder will comply with the statements made in the master file; and that the holder will inform the authorized party of any substantial change(s) to the NDI master file in advance of making such change(s).
- Responsible official signature, title, company, and contact information

VI. Listing of parties authorized to reference an NDI master file

Whenever a holder submits an LOA to the NDI master file, the holder will also submit a complete list of each party currently authorized to incorporate by reference any information in the NDI master file. This list should only contain authorized parties for which LOAs have been submitted and should be updated whenever a new LOA is submitted or when authorization is withdrawn. The list should contain the following information for each authorized party:

- Name of the authorized party
- Date of the LOA
- Specific information authorized for reference by the LOA, including section numbers and page numbers

VII. Updating information contained in an NDI master file

The holder should submit an amendment to an NDI master file whenever a change occurs that affects the accuracy of the information previously submitted in the NDI master file or when any change is made to the list of persons authorized to incorporate the NDI master file by reference. The amendment should include a cover letter specifying the change and reference the date and section or page number of any previous submission affected by the change.

Whenever an amendment is made that may affect the NDI notification of authorized parties, the holder should notify the authorized parties well before making the change and submitting the amendment in order to permit the authorized parties to supplement or amend any affected NDI notification(s) as needed.

Changes that should be submitted include, but are not limited to:

- Change to administrative information
    - Master file holder name and/or contact information
    - Contact person information
    - Agent name and/or contact information
    - Agent appointment or termination

    - List of persons authorized to incorporate the NDI master file by reference
- Change in technical information

VIII. Public availability of the information in an NDI master file

FDA should keep strictly confidential any information submitted in an NDI master file except for information that allows for the identification of existing NDI master files and their holders. FDA should maintain and regularly update a publicly available list providing only the below information:

- Name of the NDI master file holder
- Subject of the NDI master file
- NDI master file number
- Date of submission
- Status of the NDI master file

IX. Closure of an NDI master file

A holder who wishes to close an NDI master file should notify FDA and include the reason for closure. Upon closing an NDI master file, the holder should notify all parties authorized to reference the NDI master file about the closure. A closed NDI master file cannot be reviewed in support of an NDI notification. The agency may close an NDI master file that is not current or has been inactive for a period of time. FDA will notify the holder of its intent to close the NDI master file.

XI. Glossary

1. Agent: Any person who is appointed by an NDI master file holder to serve as the contact for the holder.
2. Agent Appointment Letter: A letter from an NDI master file holder that advises FDA that the holder has appointed a company/person as its agent for NDI master file purposes.
3. Authorized party: Any person who is authorized to reference an NDI master file.
4. Contact person: An employee of the NDI master file holder or agent to whom communication from FDA should be sent. The contact person may or may not be the same individual as the responsible official.
5. Letter of authorization (LOA): A letter from an NDI master file holder that authorizes a person to incorporate by reference all or part of the NDI master file's contents to support an NDI notification. The LOA also authorizes FDA to review applicable portions of the NDI master file as part of an NDI notification that references the master file.
6. NDI master file holder: A person who owns the NDI master file.
7. Person: Includes individual, partnership, and corporation.
8. Responsible official: The employee of the NDI master file holder or agent who is responsible for submitting information to the NDI master file.

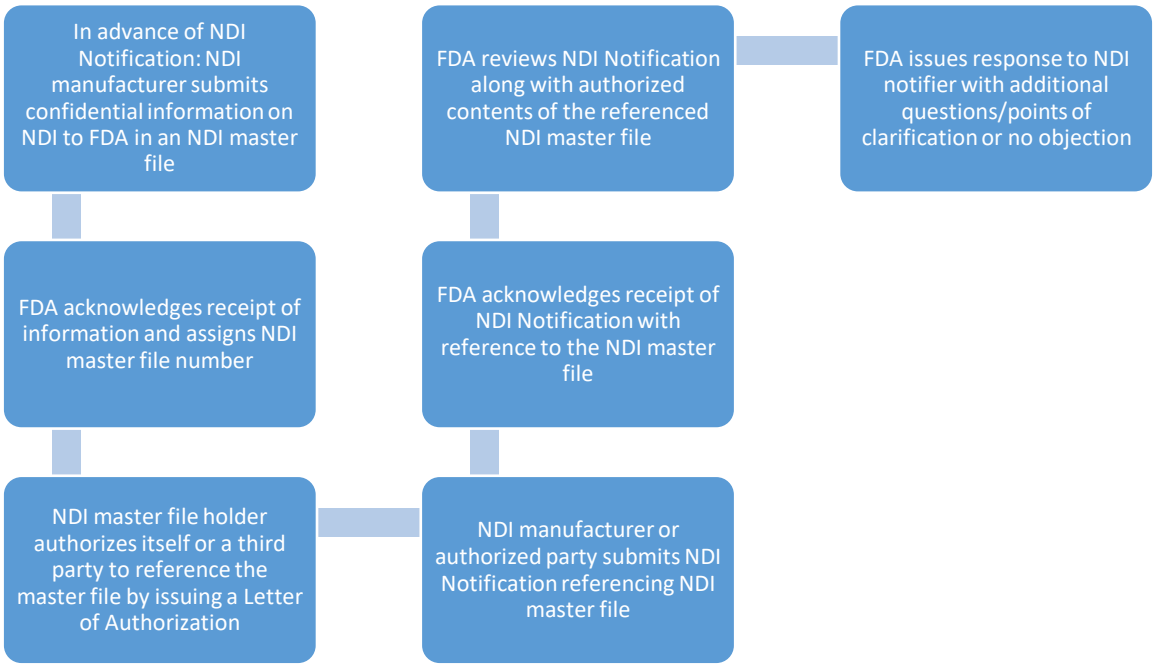
9. Subject: Title of the NDI master file.

XII. References

FDA draft guidance, *Drug Master Files Guidance for Industry*. October 2019 (accessible at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-master-files-guidance-industry).

FDA guidelines, *Drug Master Files: Guidelines*. September 1989 (accessible at https://www.fda.gov/drugs/guidances-drugs/drug-master-files-guidelines).

Annex I. Schema of the process of submitting an NDI master file and a subsequent NDI notification by the NDI master file holder or by other persons.



Annex II. NDI master file template

An NDI master file can be organized into modules, each covering different information.

Module 1: Cover Letter

Section	Content
1	**Cover Letter**
1.1	Subject of submission
1.2	Signature of NDI master file holder
1.3	Name and title of submission signer/agent

Module 2: Administrative Information

Section	Content
2	**Administrative Information**
2.1	Name and address of NDI master file holder
2.2	Name and address of manufacturer or distributor (if different from master file holder)
2.3	Name and address of submission signer/agent

2.4	Contact for FDA correspondence
2.5	References • Letter(s) of authorization • List of person(s) authorized to incorporate by reference

Module 3: General Identity and Characterization Information

Section	Content
3	**General Identity and Characterization Information**
3.1	NDI name
3.2	Nomenclature • Scientific or chemical name(s), including Latin binomial, if applicable • Common or usual name(s) • Trade name, if applicable • Plant parts, if applicable
3.3	General Properties • Physical and chemical properties • Components (including excipients), % by weight, function

Module 4: Manufacturing and Control Information

Section	Content
4	**Manufacturing information**
4.1	Raw Materials and processing aids • Raw material and processing aid specifications • Representative certificates of analysis demonstrating conformance to the specifications
4.2	Description of manufacturing process and process controls • Description of manufacturing process (e.g., process flow diagram and written description), including detailed information about the aspects of the manufacturing process that are relevant to safety and identity • Process and quality controls used in the manufacturing process
4.3	Product specifications • Specifications for the NDI • If in-house or unpublished analytical methods are used, a description of each method • Information on reference materials or reference standards that are not publicly available • Certificates of analysis demonstrating conformance to the specifications
4.4	Additional analyses • Results of additional analyses relevant to safety

4.5	Stability information • Data from stability studies and/or summary of the studies undertaken (including conditions, batches, analytical procedures) with results and conclusions
4.6	References

Module 5: Proprietary Safety Data

Section	Contents
5	**Safety information**
5.1	Unpublished/proprietary safety studies
5.2	References