

FDA Dietary Ingredient Master File Draft Guidance a Promising Step in Improving New Dietary Ingredient Notification Process, but Additional Work Remains

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On April 3, 2024, the U.S. Food and Drug Administration (FDA or Agency) Center for Food Safety and Applied Nutrition (CFSAN) released a draft guidance, “[New Dietary Ingredient Notification Master Files for Dietary Supplements](#)” (Draft Master File Guidance), that provides FDA’s recommendations for submitting and using master files for new dietary ingredient notifications (NDIN). This is the first substantive guidance issued by FDA with respect to its 2016 “[Dietary Supplements: New Dietary Ingredient Notifications and Related Issues](#)” guidance (Draft NDIN Guidance), which elicited strong reaction from industry, and follows FDA’s publication of a revised NDIN guidance dated March 5, 2024, which primarily addressed procedural steps involved in filing a NDIN.

It is interesting that FDA focused on the master file issue for its first substantive guidance on NDINs since 2016, as many other fundamental issues remain outstanding, including what triggers the NDIN requirement. That said, master files are potentially a key element in ensuring the safety of dietary supplements through a strong and efficient new dietary ingredient (NDI) notification process. Many stakeholders commenting on FDA’s Draft NDIN Guidance made this point and asked FDA to take a series of steps in moving the master file concept forward, including clarifying the role of master files to ensure that the NDIN safety review process was robust. The Draft Master File Guidance is a first step in this regard; however, there is more that FDA must do.

Importance of Master Files to Foster the Innovation of Safe Dietary Ingredients to Further Public Health

The Federal Food, Drug, and Cosmetic Act (FDCA), Section 413, requires that the manufacturer or distributor of a NDI or dietary supplement containing the NDI, submit information which supports the reasonable expectation of safe use of the NDI to FDA at least 75 days before introducing the product into interstate commerce. An NDI is defined for this purpose as a dietary ingredient that was not marketed in the United States before October 15, 1994. FDA has long taken the position that each dietary supplement containing an NDI must be the subject of an NDIN, even if the NDI has already been a subject of a NDIN from another manufacturer.

FDA's 2016 Draft NDIN Guidance proposed that a manufacturer or distributor could establish an NDI master file as a means of facilitating the filing of NDINs and marketing of the NDI in multiple dietary supplement products. Specifically, FDA proposed that manufacturers or distributors could submit a confidential NDI master file to FDA containing the manufacturing, specifications, and any information needed to describe the NDI. Other companies could reference that master file when incorporating the NDI into their product, provided they had a right of reference to do so.

In response, industry asked FDA to take the following steps to ensure that those developing NDIs would be incentivized to do the necessary safety studies to support the safe use of products containing the NDIs:

- clarify the confidential and trade secret protection of clinical studies and other data that would be part of a master file
- require that follow-on NDINs contain the same level of safety information as already-filed NDINs
- require listing of all dietary supplements entering the market so that FDA could track whether NDINs were filed as required
- take enforcement action against manufacturers marketing NDIs, or dietary supplements containing NDIs, without an NDIN

Industry pointed out that if all of these factors were in place, the master file sponsor would have de facto exclusivity for the ingredient, as they would control access to the safety data needed to market follow-on versions of the NDI. The idea was that it would be more efficient for follow-on NDI manufacturers to seek a right of reference to the master file than to do the necessary studies themselves, and more efficient for FDA than re-reviewing the science for a similar ingredient.

Limited Additional Insight From Draft Master File Guidance

The Draft Master File Guidance is limited to a discussion of mostly administrative aspects of filing a master file and does not address the additional requests made by industry. Thus the Draft Master File Guidance confirms that information included in master files is subject to existing statutory and regulatory provisions protecting trade secrets or confidential commercial information. But in contrast to the 2016 NDIN Draft Guidance, which described several types of protected information, the Draft Master File Guidance does not detail what it would consider as confidential or a trade secret.

Significantly, by not clarifying that follow-on NDINs would be held to the same safety standard as the initial filer, the Draft Master File Guidance also fails to make clear the value of a robust master file. It is unlikely that master files will become a key part of the NDIN process without this incentive to file, or to rely on, such a document. FDA should therefore confirm that follow-on NDINs will be held to the same safety standard and should articulate a mechanism and willingness to enforce against those without a right of reference, who do not file their own substantive NDIN. The NDIN requirement was included in the Dietary Supplement Health and Education Act of 1994 as a means of ensuring that safety data was on file at FDA for ingredients that are new to the U.S. market. FDA should use the master file concept as an incentivizing tool to receiving and reviewing more NDINs in an effort to protect the public health.

FDA is accepting comments until June 3, 2024.

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