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Division of Dockets Managements (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1030
Rockville, MD 20852

Re: **FDA Draft Guidance for Industry on New Dietary Ingredient Notification Master Files for Dietary Supplements ("Draft Master File Guidance")**

The Consumer Healthcare Products Association ("CHPA") is the leading national trade association representing manufacturers and distributors of over-the-counter drugs and dietary supplements. Our association is committed to maintaining the highest levels of safety in the manufacture and regulation of dietary supplements.

CHPA welcomes FDA's recent attention to the important outstanding issues associated with the new dietary ingredient notification ("NDIN") requirement under Section 413 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"). The Draft Master File Guidance represents FDA's first substantive guidance on the NDINs topic since the publication of the 2016 Draft Guidance "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" ("2016 NDIN Draft Guidance"),[1] and follows FDA's publication of a procedural guidance dated March 5, 2024, which primarily addressed steps involved in filing a NDIN.[2] CHPA appreciates this opportunity to provide comments on this Draft Master File Guidance.

FDA's 2016 NDIN Draft Guidance proposed that a manufacturer or distributor could establish an NDI master file as a means of facilitating the process for multiple parties to file NDINs for the same or related new dietary ingredients.[3] As described by FDA in the 2016 NDIN Draft Guidance, the idea was that a manufacturer or distributor could submit a confidential NDI master file to FDA containing manufacturing information, specifications, and any clinical or safety data needed to support the safety of a NDI.[4] After accepting the NDI master file, FDA

[1] FDA, Draft Guidance for Industry: New Dietary Ingredient Notifications and Related Issues (Aug. 2016) ("2016 NDIN Draft Guidance").
[2] FDA, Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes (Mar. 5, 2024).
[3] 2016 NDIN Draft Guidance at 28-29.
[4] *Id*.

would publish a list of all such NDI master files that it had received by the owner, so that other manufacturers and distributors could be aware of the existence of the master files. Manufacturers and distributors planning to market the same NDI or a dietary supplement containing the same NDI could then contact the master file owner, identified on the list, to request a letter of authorization to rely on the master file to satisfy their own NDIN requirement. Relying on an existing NDI master file would allow that subsequent manufacturer or distributor to efficiently meet the NDIN requirement, without the burden of generating scientific or clinical data on their own.

CHPA supports the establishment of a master file system for NDINs, as described in our comment to the 2016 NDIN Draft Guidance.[5] CHPA views the master file system as an important component of a comprehensive framework to ensure the safety of dietary supplements containing NDIs, as envisioned by the drafters of the Dietary Supplement Health and Education Act of 1994 (DSHEA). As CHPA made clear in its 2016 comments,[6] FDA must take a number of actions, as follows, to ensure that those developing NDIs are incentivized to do the necessary safety studies to support the safe use of products containing the NDIs.

- First, FDA must be clear that follow-on NDINs that do not reference a master file must contain the same level of safety information as already-filed NDINs. FDA enforcement of this requirement will ensure that master files become an important element in meeting the NDIN requirement;
- Second, FDA must consistently take enforcement action against manufacturers marketing NDIs, or dietary supplements containing NDIs, without an NDIN;
- Third, FDA should state explicitly that unpublished clinical and other data submitted to a NDI master file would be treated as confidential and subject to trade secret protection. Such protection will incentivize industry to invest in the important but costly studies to support safety; and
- Fourth, FDA must clarify that NDI master files will be reviewed for completeness even when there is no corresponding NDIN.

CHPA applauds FDA for taking the initial step of publishing a separate draft guidance to clarify the use of master files in supporting NDINs. Allowing parties to rely on an NDI Master File established by a previous party has the potential to reduce unnecessary duplicative

[5] CHPA Comments to FDA on Draft Guidance, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, 81 Fed. Reg. 53486, Docket No. FDA-2011-D-0376 (Dec. 12, 2016) ("CHPA Comment to FDA on 2016 NDIN Draft Guidance").
[6] *See* CHPA Comments to FDA on 2016 NDIN Draft Guidance at 1-3.

submissions from ingredient suppliers, dietary supplement manufacturers and distributors and therefore to facilitate a more robust adherence to the NDIN requirement. Moreover, the requirement of written authorization for reliance on NDI master files creates a potentially meaningful incentive for master file owners to invest in rigorous safety studies. Such master file owners may, in this way, obtain some benefit from the investment they make in ensuring adequate safety and clinical data for an NDI.

Unfortunately, the Draft Master File Guidance is incomplete, and does not do enough in describing the master file system. CHPA urges FDA to revise the guidance to address a number of key issues to ensure that master files serve the purpose of supporting the safety of dietary supplement products. We outline the revisions and additions that are necessary here.

- **The Draft Master File Guidance Must State Explicitly That All NDINs Will Be Held to the Same Safety Standard**

The NDIN requirement was included in DSHEA as a means of ensuring that safety data was on file at FDA for ingredients that are new to the U.S. market. FDA has consistently interpreted this requirement, in FFDCA 413(a), to mean that an additional NDIN must be filed by each distinct manufacturer or distributor of a dietary supplement containing the new dietary ingredient. As stated in CHPA's comment on the 2016 NDIN Draft Guidance, CHPA believes that this ingredient-focused approach helps to ensure that all entities marketing a dietary supplement with the NDI are actually using the same ingredient.[7] In addition, requiring a separate NDIN from each entity introducing the NDI to the market serves the important purpose of providing FDA with an accurate record of entities marketing NDIs.

This requirement is only effective in ensuring safety, however, if FDA is explicit in requiring that each and every NDIN filed must contain "evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe."[8] This would be satisfied by either referencing a master file or providing the same level of safety data as any previously filed NDIN for the same substance.

Significantly, failing to clarify in the Draft Master File Guidance that follow-on NDINs without a formal master file reference would be held to the same safety standard as any original NDIN

[7] CHPA Comments to FDA on 2016 NDIN Draft Guidance at 19.
[8] 21 U.S.C. § 350b(a)(2).

substance leaves the value of a robust master file in doubt. It is unlikely that master files will become a key part of the NDIN process and improve the rate of submissions without FDA holding every NDIN to the same high standard. FDA should therefore confirm that follow-on NDINs not referencing a master file will be held to the same safety standard and articulate a mechanism and willingness to enforce against those without a right of reference, who do not file their own substantive NDIN.

- **FDA Must Make Clear That It Will Take Enforcement Against Marketing NDIs, or Dietary Supplements Containing NDIs, Without an NDIN.**

The NDIN requirement is only meaningful if FDA consistently takes enforcement action against manufacturers and distributors who market dietary supplements containing new dietary ingredients without having filed a NDIN. Even small differences in ingredients can alter safety profiles, potentially jeopardizing consumer safety. Rigorous enforcement against follow-on NDIs without an NDIN mitigates risks associated with novel ingredients by ensuring that all finished dietary supplement manufacturers source NDIs that that adhere to safety standards and have been reviewed by FDA, whether in a standalone submission or a master file. Without such enforcement, companies can more easily circumvent regulatory requirements, leading to inconsistencies in safety assessments and potentially harmful products entering the market. By holding accountable those who fail to provide or are unauthorized to reference appropriate safety data for their ingredients, the FDA will safeguard public health and will bolster consumer confidence in the safety of dietary supplements.

- **FDA Must Clarify That Scientific and Clinical Studies Submitted In a NDI Master File Would Be Treated as Confidential Commercial Information or as Trade Secret**

The master file system only works as a component of ensuring dietary supplement safety if FDA makes clear that unpublished scientific and clinical studies submitted to the master file will be regarded as confidential commercial information (CCI)[9] and trade secret[10] under FDA regulations. The confidentiality of a master file means that the master file owner is the *only* entity that can rely on the master file to support a NDIN *unless and until* a subsequent manufacturer or distributor obtains permission from the master file owner to also rely on the data in the master file. As such, the master file owner gains a period of *de facto* exclusivity

[9] 21 CFR § 20.61(b).
[10] 21 CFR § 20.61(a).

once they have successfully filed a NDIN. This *de facto* exclusivity serves as a powerful incentive for entities to invest in the necessary safety studies.

In the 2016 NDIN Draft Guidance, FDA suggested that permission would be required for a subsequent party to rely on "any non-public safety data" contained in a master file.[11] However, in the same 2016 NDIN Draft Guidance FDA stated that "history of use or other safety information related to the NDI or the dietary supplement, including both published and unpublished studies" is generally not trade secret or confidential information.[12] CHPA pointed to this inconsistency in its comments on the 2016 Draft NDIN Guidance,[13] and pointed out that FDA's position on unpublished studies was inconsistent with 21 CFR § 20.61(a), which defines "trade secret" as "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." Safety studies on innovative ingredients provide the data, and thus the basis, on which to develop and potentially market an innovative dietary ingredient. There is no question that such studies require innovation and substantial effort at a significant cost[14]. CHPA noted further the FDA's position was inconsistent with how such studies are treated in the drug context where FDA does not regard unpublished safety studies as releasable information.[15]

In its comment on the 2016 NDIN Draft Guidance, CHPA urged FDA to clarify that unpublished data and studies would be treated as CCI and trade secret.[16] Unfortunately, the Draft Master File Guidance does not detail what it would consider as confidential or a trade secret in Section III.A.4, and instead states "there is no presumption that any particular information in the Master File is trade secret information or CCI." CHPA urges FDA to revise Section 4 of the Draft Master File Guidance to explicitly recognize unpublished studies as falling within the trade secret definition and to stipulate that reliance on "non-public safety data" from an NDI Master File necessitates signed authorization from the Master File owner.

[11] 2016 NDIN Draft Guidance at IV.C.5.
[12] *Id*. at 52.
[13] CHPA Comments to FDA on 2016 NDIN Draft Guidance at 17.
[14] Dietary supplement trade associations estimate $25,000 - $500,000 per ingredient to conduct all studies and generate the NDIN dossier for a new ingredient. Available at: *https://www.nutritionaloutlook.com/view/would-fdas-ndi-guidance-really-cost-industry-billions-dollars*
[15] *Id*.
[16] CHPA Comments to FDA on 2016 NDIN Draft Guidance at 18.

- **FDA Must Clarify That NDI Master Files Will Be Reviewed for Completeness Even When There is No Corresponding NDIN**

FDA states in Section III.D.1 of the Draft Master File Guidance that it will only conduct a substantive review of a master file once there is a corresponding NDIN, and that it "does not intend to conduct a scientific review of an NDIN Master File" before that time.[17]

In most cases, this approach is sufficient because a master file will be submitted with a corresponding NDIN, and thus FDA will review the master file as part of the NDIN review. However, there may be rare instances in which a NDI master file is established *without* a corresponding NDIN being filed. In those cases, there will be no way for other manufacturers and distributors to know if the NDI master file will provide a sufficient basis to support a NDIN.

For this reason, CHPA urges FDA to modify section III.D.1 of the Draft Master File Guidance. Section III.D.1 should contain text stating that FDA will conduct a review of a NDI Master File for completeness in the rare instances when a NDI master file is submitted without a corresponding NDI. A review for completeness would be intended to ascertain whether "considering the information cited from the NDIN Master File . . . there is evidence of safety establishing that the NDI" when used as a standalone dietary component under specified conditions of use and target population, will reasonably be expected to be safe.[18]

This clarification would be helpful to signal to manufacturers and distributors that a NDI master file is likely adequate to support a NDIN, even when a NDIN has not been reviewed for the NDI. This signal will further the likelihood that such manufacturers and distributors would seek authorization to rely on the NDI master file and adds further to the incentives for parties to establish master files with FDA.

Conclusion

A well-executed master file system stands to benefit both industry stakeholders and the FDA, fostering increased NDI submissions, bolstering public safety, and stimulating innovation and scientific investments. Ultimately, this framework should incentivize companies to augment

[17] FDA, Draft Guidance for Industry: New Dietary Ingredient Notification Master Files for Dietary Supplements (Apr. 2024) at 7.
[18] *See* 21 U.S.C. § 350b(a)(2).

research investments demonstrating the safety of new ingredients and final products. While this Draft Master File Guidance sets the stage, FDA needs to do more to get companies interested in filing.

Respectfully submitted,

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