GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

July 19, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Submitted via www.regulations.gov

RE: *Draft Guidance for Industry: Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-market Notification*, 87 Federal Register 30843 (20 May 2022); Docket No. FDA-2022-D-0281

To Whom It May Concern:

GOED, the Global Organization for EPA and DHA Omega-3s, represents the worldwide EPA and DHA omega-3 industry, with a mission to increase consumption of EPA and DHA omega-3s around the world. The membership is built on a quality standard unparalleled in the market and members must comply with quality and ethics guidelines that ensure members produce quality products that consumers can trust. Our 160+ members represent the entire supply chain of EPA and DHA omega-3s, from fisheries and crude oil suppliers to refiners, concentrators and finished product brands.

GOED thanks the Agency for the opportunity to provide comments on the *Draft Guidance for Industry: Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-market Notification.*[1] While GOED appreciates the Agency's efforts and good intentions, we believe this draft guidance is premature given that the 2016 *Draft Guidance for Industry: New Dietary Ingredient Notifications and Related Issues*[2] has yet to be finalized.

GOED believes the major sources of EPA- and DHA-rich oils are being lawfully sold as components of dietary supplements due to the fact that they have been marketed as dietary ingredients prior to October 15, 1994, are GRAS for intended uses, or have filed New Dietary Ingredient (NDI) notifications with the FDA. Thus said, while this new draft guidance is applicable to only a limited number of GOED members, unanswered questions from the last draft guidance documents make it difficult for these members to know if an NDI notification should be filed with the FDA. For this reason, we do not believe the 2022 draft guidance should be finalized before the 2016 draft guidance. Once the 2016 draft guidance is finalized, GOED

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-policy-regarding-certain-new-dietary-ingredients-and-dietary-supplements?utm_medium=email&utm_source=govdelivery
[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues

would like to see the Agency take proper enforcement action when warranted. Until that happens, GOED does not support the finalization of the 2022 draft guidance.

Rather than reiterate GOED's past comments that have yet to be addressed by the Agency, GOED has attached a copy of our comments from the 2016 draft guidance, as well as those we submitted in 2011 in response to the original draft guidance.

Thank you in advance for your consideration of our feedback.

Sincerely,

Harry B. Rice, Ph.D.
Vice-President, Regulatory & Scientific Affairs

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GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

December 12, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry*, 81 Federal Register 53486 (August 12, 2016); Docket No. FDA-2011-D-0376

Dear Sir or Madam:

The Global Organization for EPA and DHA Omega-3s (GOED) is an association of processors, refiners, manufacturers, distributors, marketers, retailers and supporters of products containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids. GOED is extremely interested in ensuring that consumers continue to have access to safe, high quality EPA and DHA products. Thus said, GOED thanks the Agency for its work over the last five years to revise *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry* and we appreciate the opportunity to provide the comments found below.

General Comments about the Fish Oil Industry

While the market for EPA- and DHA-rich dietary supplements has exploded since the passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994, with growth being driven by positive results from high-quality scientific investigations, the first fish oil was launched back in 1760 in the United Kingdom. In 1790, the cod liver oil known as Scott's Emulsion was launched in the United States. Over 200 years later, Scott's Emulsion continues to be marketed, thus representing what GOED believes to be the oldest continuously marketed dietary supplement in the United States. In addition to cod liver oil, prior to October 15, 1994, multiple forms of fish oil were launched, including fish body oil, concentrates (both ethyl esters and triglycerides) and salmon oil. In common to all past and present omega-3-rich oils is that their primary composition is EPA, DHA and a mixture of minor fatty acids.

For years, EPA- and DHA-rich omega-3 oils have been sourced from multiple organisms and species. Since the FDA issued its Final Rule on June 5, 1997 (62 FR 30751) affirming menhaden oil as generally recognized as safe (GRAS) with limitations on the maximum use levels in specific food categories in order to ensure that daily intakes of EPA+DHA did not exceed 3.0 grams per day, EPA and DHA have been considered the valuable components to which these oils are standardized, and the products are principally comprised of EPA, DHA and a mixture of fatty acids. Subsequent to the Final Rule, more than 10 companies wishing to market their fish oils for addition to food have received letters of no objection from the FDA. Despite minor differences among the oils in fatty acid composition, FDA has raised no potential safety issues given that all companies indicated that intake of EPA+DHA would not exceed 3.0 grams per day. From a whole food perspective, consider

that a single serving of salmon contains more EPA, DHA and a range of other minor fatty acids than most fish oil supplements on the market.

GOED believes the major sources of EPA- and DHA-rich oils are being lawfully sold as components of dietary supplements due to having been marketed as dietary ingredients prior to October 15, 1994, are GRAS for intended uses, or have filed New Dietary Ingredient (NDI) Notifications with the FDA.

GOED understands the need for the Guidance to be general in nature so that it applies to the entire dietary supplement industry, but consideration should be given to expanding or to bring clarity to the Guidance in order to provide more detailed direction to specific segments of the industry. This has the potential to result in fewer inquiries directed to the FDA. Given the long history of safe use (demonstrated in part by the limited number of reports in the adverse event reporting system) of EPA- and DHA-rich ingredients, GOED urges the FDA to provide clarification on issues of concern to the omega-3 industry, as outlined below.

Esterification

Review of the patent landscape reveals that the process of esterifying fish oils, as part of the process to concentrate or purify EPA and DHA from fish oils, was being used prior to October 15, 1994. While this is not evidence that concentrated fish oils using this technology have been marketed as dietary ingredients prior to 1994, the information provides evidence that many companies perceived fish oils as valuable commercial products warranting IP protection as early as the 1980s. In addition, it demonstrates that the technologies and methods used to produce concentrated fish oils *via* esterification existed and were being optimized in the 1980s and early 1990s.

Examples of early patents in this area include, but are not limited to:

- U.S. patent 4,377,526 *Method of purifying eicosapentaenoic acid and its esters*
  - Filed December 11, 1981 / Published March 22, 1983
  - Assignee: Nippon Suisan Kaisha, LTD
- U.S. Patent 4,792,418 *Method of extraction and purification of polyunsaturated fatty acids from natural sources*
  - Filed December 19, 1985 / Published December 20, 1988
  - Assignee: Century Laboratories, Inc.
- U.S. Patent 4,966,734 *Deodorization of fatty ester mixtures*
  - Filed March 16, 1989 / Published October 30, 1990
  - Assignee: BASF Aktiengesellschaft
- U.S. Patent 5,130,061 *Processes for the extraction of polyunsaturated fatty acid esters from fish oil*
  - Filed May 24, 1989 / Published July 14, 1992
  - Assignee: Innova Di Ridolfi Flora & C. S.A.S.

While GOED has documentation that omega-3 ethyl esters from fish oil were on the market prior to October 15, 1994, such documentation does not necessarily exist for each unique product currently being sold; however, the absence of documentation for each unique omega-3 ethyl ester from fish oil currently on the market should not yield an NDI requiring an NDI Notification, given the widespread and evidenced use of such oils in general prior to October 15, 1994. GOED would like clarification from FDA on this aspect.

Moreover, the following two questions and answers in the Guidance seem to provide two opposite positions on the potential status of omega-3 ethyl esters from fish oil. For the sake of clarification, GOED recommends some minor rewording of the second answer.

Question 1: "What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not result in chemical alteration?" (Page 27)
Answer 1: "In general, FDA considers a process that does not result in chemical alteration to mean a process that: (1) involves an ingredient composed of one single raw material, or derived from a single raw material using a manufacturing process that involves only physical steps (e.g., water extraction and condensation); and (2) does not involve attempts to selectively increase the concentration of particular active ingredients or cause a chemical reaction (other than **esterification**) that would modify the covalent bonds of any substance in the original material. This type of process is unlikely to affect the safety profile of the ingredient in question or of dietary supplements containing the ingredient."

GOED's interpretation of the above is that the FDA is supportive of the use of esterification for the purpose of manufacturing omega-3 ethyl esters from fish oil. For this purpose, the esterification process simply aims to standardize the content of EPA and DHA, two fatty acids that have a long history of safe use. In addition, as fish oil concentrates were on the market prior to October 15, 1994, it is expected that esterification to produce concentrates of EPA and DHA sold as omega-3 ethyl esters of fish oils will not be considered a novel process to selectively increase the concentration of these constituents, and hence would not be classified as chemical alteration.

Question 2: "If I alter the chemical structure of a dietary ingredient, is the new substance still a dietary ingredient?" (Page 41)
Answer 2: "It depends. Altering the chemical structure of a dietary ingredient (e.g., creation of new stereoisomers, addition of new chemical groups as in **esterification**) creates a new substance that is different from the original dietary ingredient. The new substance is not considered to be a dietary ingredient merely because it has been altered from a substance that is a dietary ingredient and, therefore, is in some way related to the dietary ingredient."

Clearly, this question and answer is not meant to exclude esterification of fish oil which yields a specific concentration of ethyl esters of EPA and DHA, two fatty acids that have a long history of safe use. The simple esterification of EPA and DHA uses ethanol to provide the ethyl group, and ethyl esters of EPA and DHA would not be considered new as they have been present in dietary supplement products marketed before October 15, 1994 as detailed above. In addition, ethanol is a

solvent noted by the FDA in the Guidance as NOT "extracting different types of constituents". It was also noted that "FDA generally regards extraction that includes a filtration step or that involves the use of a solvent other than water or alcohol (aqueous ethanol) as a process that chemically alters the source ingredient and therefore triggers the NDI notification requirement for the resulting dietary ingredient. By default, it appears that given the use of ethanol for the manufacture of omega-3 ethyl esters from fish oil, FDA does not view esterification using ethanol as a process that chemically alters the source ingredient, and thus would not trigger the NDI Notification requirement for the resulting dietary ingredient.

GOED requests the FDA to clarify that an ingredient produced via esterification for the purpose of concentrating or purifying EPA and DHA to produce omega-3 ethyl esters does not yield an NDI. GOED notes that on page 28 of the Guidance, it states, "We are willing to consider arguments supported by science demonstrating that particular manufacturing processes do not actually result in a chemical alteration or have any effect on the safety profile of the ingredient." Should additional information be required to solidify your position on esterification of fish oil, please do not hesitate to ask.

Concentration

As mentioned before, all omega-3 rich oils are composed primarily of EPA, DHA and a mixture of minor fatty acids. The various means of concentrating EPA and DHA (e.g. urea, distillation, chromatography and enzymatic separation) are essentially just removing some of the fatty acids from that composition. As such, the various means of concentrating EPA and DHA are essentially just removing some of the fatty acids from that composition.

Distillation and Filtration

GOED notes on page 25 that the FDA points to distillation and filtration, two common processing steps for omega-3 rich oils, as yielding a chemical alteration and thus the potential need to file an NDI Notification. For the omega-3 industry, filtration is used to physically separate a solid from a liquid and distillation (i.e. molecular) is used to remove contaminants that may be present in the oil. These simple processes of distillation and filtration to produce and/or purify an oil extract are different than what is anticipated FDA considers as contributing a chemical alteration, as they do not significantly change the identity of the ingredient In order to avoid confusion for the omega-3 industry, GOED requests the FDA to provide clarification for this Q and A to differentiate necessary distillation and filtration steps involved in traditional extraction and/or purification of oils from such steps that may actually be novel and might produce chemical alteration of a dietary ingredient. Processes like distillation and filtration, along with others, are used in the vegetable oil refining industry. This is an important point because the FDA does not consider a filtered vegetable oil to have a different safety profile requiring notification, so it shouldn't require a filtered omega-3-rich oil to be notified.

Supercritical Fluid Extraction

On page 34, the Agency notes that supercritical fluid extraction "…was not commonly used prior to 1994." GOED disagrees with this assertion and we are providing the following non-exhaustive list of references to support our position specific to the omega-3 industry.

- Hierro M.T.G. and Santa-Maria G., 1992. Supercritical fluid extraction of vegetable and animal fats with CO_2 – A mini review. Food Chemistry, 45: 189-192.

- Higashidate, S., Y. Yamauchi and M. Saito, 1990. Enrichment of eicosapentaenoic acid and docosahexaenoic acid esters from esterified fish oil by programmed extraction-elution with supercritical carbon dioxide. J. Chromatography, A515: 295-303.

- Latta, S., 1990. Supercritical fluids attracting more interest. INFORM, 1: 810-816.

- McHugh M.A., Krukonis V.J. and Brenner H., 1994. Supercritical Fluid Extraction (Second Edition) Principles and Practice. Boston: Butterworth-Heinemann ISBN: 978-0-08-051817-6.

- Nilsson, W.B., E.J. Gauglitz Jr., J.K. Hudson, V.F. Stout and J. Spinelli, 1988. Fractionation of menhaden oil ethyl esters using supercritical fluid CO_2. J. Am. Oil Chem. Soc., 65: 109-117.

- Stahl E, Quirin KW and Gerard D (1987) Dense Gases for Extraction and Refining. New York: Springer-Verlag.

- U.S. Patent 4,466,923 *Supercritical CO_2 extraction of lipids from lipids containing materials*
  - Filed April 1, 1982 / Published August 21, 1984
  - Assignee: The United State of America as Represented by the Secretary of Agriculture

- U.S. Patent 4,692,280 *Purification of fish oils*
  - Filed December 1, 1986 / Published September 8, 1987
  - Assignee: The United State of America as Represented by the Secretary of Commerce

- U.S. Patent 4749522 *Supercritical fluid extraction of animal derived materials*
  - Filed October 31, 1985 / Published June 7, 1988
  - Assignee: Angio-Medical Corporation

<u>Manufacturing Changes</u>

Manufacturing changes used to make the same product on the market (i.e. no change to the identity of the dietary ingredient), either before 1994 or after submission of an initial NDI Notification, should not yield an NDI. These manufacturing changes should be addressed by Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Final Rule. GOED agrees that the focus of FDA guidance should be on whether or not a change to the manufacturing process alters the safety profile or identity of the ingredient and not be specific to the manufacturing change itself. After all, the principal product produced is

always an omega-3 rich-oil, with the predominant fatty acids being EPA and DHA, along with a mixture of minor fatty acids.

Over time, the omega-3 industry has learned how to further reduce contaminant levels. By all accounts, this is a positive outcome, resulting in safer dietary ingredients without any alteration to their identity. GOED requests clarification of the following question and answer on page 20 so that it doesn't appear as if the reduction in contaminant levels will yield an NDI.

Question: "If I change the manufacturing process for a dietary ingredient that was marketed in the U.S. prior to October 15, 1994, does that make the ingredient an NDI?" (Page 20)
Answer: "The answer depends on the extent to which the manufacturing process change affects the resulting ingredient. As discussed in a separate FDA guidance on manufacturing changes, such changes may affect the identity of the food substance or its safety and suitability for certain conditions of use. Manufacturing changes may also affect the purity of a food substance, such as the amounts of impurities and contaminants in the food substance."

GRAS
In the first draft guidance for industry issued July 2011, there was reference to self-affirmed GRAS ingredients being exempt from the need to submit an NDI Notification. In the revised draft guidance for industry, there's no mention of self-affirmed GRAS. GOED asks for the reinstatement of the statement that self-affirmed GRAS ingredients are exempt from the need to submit an NDI Notification.

Abbreviated NDI Process for Certain Ingredients
If a company determines its product requires an NDI Notification, a separate matter is the kind of data that would be required to substantiate the safety, whether it just be data on a safe history of use or more detailed toxicology studies. GOED notes that the FDA specifically mentioned fish oil as an example in a question and answer found on pages 68-69.

Question: "What data and information should I submit to substantiate an NDI's history of safe use?"
Answer: "As another example, if your NDI is an oil made from a plant or fish and you can show that the oil consists only of a mixture of fatty acids, each of which you can identify and demonstrate to be widely consumed at higher levels in conventional foods, you may be able to conclude that the dietary supplement containing the NDI will reasonably be expected to be safe based on compositional information alone."

For companies planning to market omega-3 (EPA/DHA) rich ingredients that can satisfy the aforementioned, GOED believes a mechanism should be in place for such companies to submit an abbreviated dossier. One idea is for GOED to provide the FDA with a "master file" of information that any omega-3 company needing to submit an NDI Notification can refer to in order to satisfy the history of safe use. Theoretically, this may not be necessary given the existing GRAS affirmation from the FDA from 1997 on menhaden oil which could be used to substantiate a safe history of use for any oil containing lower levels of fatty acids (EPA/DHA) than the highest dose in the petition.

GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

Pre-DSHEA (Grandfathered) Dietary Ingredients

GOED encourages the creation of a list of grandfathered ingredients, which would provide a 'safe harbor' from the NDI Notification requirements. We have a considerable amount of documentation that various fish oils and omega-3-rich oils, including omega-3 ethyl esters, were marketed prior to October 15, 1994. At this point, it's not clear how and to whom GOED should provide this documentation for consideration in a list of "grandfathered" dietary ingredients. GOED requests the FDA provide further direction on this effort.

Thank you in advance for your consideration of our feedback.

Sincerely,

Harry B. Rice, Ph.D.
Vice-President, Regulatory & Scientific Affairs

GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

November 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Docket No. FDA-2011-D-0376

Dear Sir or Madam:

The Global Organization for EPA and DHA Omega-3s (GOED) is an association of processors, refiners, manufacturers, distributors, marketers, retailers and supporters of products containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids. GOED's membership represents a broad range of businesses, from small entrepreneurs to multinational food companies. The Organization's objectives are to educate consumers about the health benefits of EPA and DHA by collaborating with government groups, the healthcare community and the industry, while setting high standards for our business sector. GOED is extremely interested in ensuring that consumers continue to have access to safe, high quality EPA and DHA products and appreciates the opportunity to provide comments in response to the July 1, 2011 publication of "Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" ("Guidance").

General Comments about the Fish Oil Industry

While the market for EPA- and DHA-rich dietary supplements has exploded since the passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994, with growth being driven by positive results from high-quality scientific investigations, the first fish oil was launched back in 1760 in the UK. In 1790, the cod liver oil known as Scott's Emulsion was launched in the United States. Over 200 years later, Scott's Emulsion continues to be marketed, thus representing what GOED believes to be the oldest continuously marketed dietary supplement in the United States. In addition to cod liver oil, prior to October 15, 1994, multiple forms of fish oil were launched, including fish body oil, concentrates (both ethyl esters and triglycerides) and salmon oil.

For years, EPA- and DHA-rich omega-3 oils have been sourced from multiple organisms and species. Since the FDA issued its Final Rule on June 5, 1997 (62 FR 30751) affirming menhaden oil as generally recognized as safe (GRAS) with limitations on the maximum use levels in specific food categories in order to ensure that daily intakes of EPA and DHA did not exceed 3.0 grams per day, EPA and DHA have been considered the valuable components to which these oils are standardized. Subsequent to the Final Rule, more than 10 companies wishing to market their fish oils for addition to food have received letters of no objection from the FDA. Despite minor differences among the oils in fatty acid composition, FDA raised no potential safety issues given that all companies indicated that intake of EPA + DHA would not exceed 3.0 grams per day.

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While GOED believes the major sources of EPA- and DHA-rich oil are being lawfully sold due to having been marketed as dietary ingredients prior to October 15, 1994, are GRAS for intended uses, or have filed (without objection) NDI Notifications with the FDA, GOED respectfully requests the FDA to consider the following comments when finalizing the Guidance.

1. By creating unreasonable regulatory barriers for companies marketing dietary ingredients that are not only safe, but provide health benefits to Americans, the Guidance is blatantly disregarding the Congressional findings delineated in Section 2 of DSHEA, which provide the best available record of Congressional intent. GOED encourages the FDA to review this section. Of particular concern is the disregard for the following:

- "preventive health measures, including … appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures"
- "consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements" Note that since the passage of DSHEA, there has been increasing clinical research demonstrating the benefits of dietary supplements. In particular, more than 2,500 randomized controlled trials have been conducted in humans using EPA and DHA products, many focused on preventive care in healthy individuals.
- "the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers"
- "dietary supplements are safe within a broad range of intake, and safety problems with dietary supplements are relatively rare"
- "the nutritional supplement industry is an integral part of the economy of the United States"

GOED Recommendation: GOED encourages the FDA to revise the Guidance according to Congressional intent. In the absence of significant revisions, the Guidance, as currently written, would restrict consumer access to safe nutritional supplements, like EPA and DHA omega-3s, which in turn would have a detrimental impact on the American economy, as well as on the health of its citizens. Consider that in 2005, 84,000 deaths were attributed to low intake of omega-3 (EPA + DHA) fatty acids.[1]

2. Congress intended notifications to be submitted for the ingredient, not each finished product using the ingredient. FDA's Guidance does not reflect the statutory language of DSHEA. That is, the Guidance indicates that New Dietary Ingredient Notifications (NDINs) are required for dietary supplements containing a NDI, even if the dietary ingredient was the subject of a NDIN for which FDA acknowledged no objection. The requirement for individual supplement companies to file a NDIN with the FDA for multiple products containing ingredients already notified is not only redundant, but unnecessarily burdensome. This

[1] Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, et al. (2009) The Preventable Causes of Death in the United States: Comparative Risk Assessment of Dietary, Lifestyle, and Metabolic Risk Factors. PLoS Med 6(4): e1000058. doi:10.1371/journal.pmed.1000058.

requirement conflicts with Congressional intent to protect consumer choice and presents unreasonable regulatory barriers slowing the flow of safe products to consumers.

FDA's attempt to extend the NDI notification requirement to all dietary supplements that contain a NDI is inconsistent with other positions the Agency has taken on this issue over the past 17 years since the enactment of DSHEA. In promulgating rulemaking to implement this section of DSHEA, the agency estimated that the number of NDINs that would be filed annually would be between zero and 12.[2] Paradoxically, the Agency has estimated the number of new dietary supplements that are introduced each year to be 2,900.[3] Even though these new supplements may include products that consist only of old dietary ingredients (ODIs), it seems clear that the Agency was not assuming during the rulemaking process that NDINs would be submitted for all dietary supplements.

GOED Recommendation(s): GOED recommends the Guidance be revised in accordance with Congressional intent of being ingredient-, not supplement-specific. If Congress had intended for the notifications to be supplement-, not ingredient-specific, why is the regulation to enable industry to comply with the requirements of the DSHEA entitled "Premarket Notification for a New Dietary Ingredient"?

If the Agency, upon further consideration, should not agree with GOED's interpretation, we would ask that serious consideration be given to implementing a modified master file-like process similar to that used by Canada's Natural Health Products Directorate. GOED believes the master files should be broad enough to encompass "classes" of products. For example, while dietary supplements inclusive of fish oil concentrates (ethyl esters and triglycerides) should not be required to file NDINs because fish oil concentrates were marketed prior to October 15, 1994, in the unlikely event that a determination was made to the contrary, GOED supports the writing of a master file for all ethyl ester or triglyceride concentrates up to a maximum daily intake level of 2.0 grams EPA + DHA per day for dietary supplements.[4]

3. The Guidance indicates that manufacturing changes will "most likely" result in the need for a NDIN. The Guidance further states that changes to the chemical composition of the ingredient would require a NDIN. We feel the FDA has failed to recognize that natural products like edible oils and herbal extracts often contain a large number of unique chemical substances, and that the ratios of each substance can vary significantly as a result of environmental and seasonal influences. For example, the fatty acid profile of oils derived from edible marine species can change significantly due to environmental influences (e.g. water temperature, etc…), effects of diet and seasonal variation (e.g. migration).[5] These changes in chemical composition can be experienced lot-to-lot and season-to-season. The Guidance can be interpreted to mean that such changes require lot-by-lot notification to the FDA.

[2] Federal Register 62 (23 Sept 1997): 49886-49892
[3] Federal Register 76 (3 June 2011): 32215-32217
[4] Docket No. 2003Q-0401
[5] Fish Feed Technology: Lectures Presented at the FAO/UNDP Training Course in Fish Feed Technology, held at the College of Fisheries, University of Washington, Seattle, Washington, U.S.A., 9 October-15 December 1978. Rome: Food and Agriculture Organization of the United Nations, 1980. http://www.fao.org/docrep/x5738e/x5738e05.htm.

GOED Recommendation: We propose FDA establish notification expectations similar to those existing for other regulated products. For example, changes to a medical device manufacturing process require premarket notification to the FDA only if they impact the safety and effectiveness of the product. The Guidance does not allow for industry to make similar judgments about the products they market, rather the Guidance suggests that only FDA may make these decisions. If FDA's position is that chemical composition changes as described above should be notified, then this position contradicts the findings of Congress in Section 2 of the DSHEA when they stated that "dietary supplements are safe within a broad range of intake, and safety problems with supplements are relatively rare." This requirement is also contradictory to congressional intent to prevent unreasonable regulatory barriers for safe products.

4. The Guidance indicates the type of documentation required to demonstrate that a dietary ingredient was marketed as a dietary supplement ingredient prior to October 15th, 1994. GOED believes the scope of documentation suggested by FDA is too narrow and should be broadened. Consider the following:

a) The documentation proposed by FDA would now be greater than 17 years old and many companies will not have retained these historical records.

b) Finding examples of surviving documentation will be exceedingly difficult. In 1994, digital imaging and sharing of electronic data via the internet was uncommon. Consequently, today's electronic search tools and internet sites are less powerful for the retrieval of pre-1994 records concerning the commercialization of supplements. Finding such documentation through this electronic medium will prove to be challenging and burdensome.

c) The current language in the draft guidance suggests that each dietary supplement company would have a legal obligation to affirm, with pre-DSHEA documentation (*i.e.,* before October 15, 1994), that its products contain only ODIs. If that were the case, every manufacturer could have a separate obligation to prove their ingredients were on the market pre-DSHEA. This is burdensome and particularly disadvantageous for newer members of the industry who would not have pre-DSHEA records.

d) The Guidance indicates "If the changes in your manufacturing process alter the chemical composition or structure of the ingredient, the resulting compound is probably a NDI and a notification to FDA would be required." So, not only is it necessary to prove that an ingredient was marketed prior to October 15, 1994, there is an additional burden to demonstrate that the manufacturing process has not changed. FDA's position that a change in the manufacturing process "most likely" means a change in the regulatory status represents a new burden to industry. As such, it is extremely unlikely that any company has maintained 17 year old manufacturing documentation to match with their proof of marketing data, particularly when one considers that in 1994 Good Manufacturing Practices and corresponding documentation requirements were not required of dietary ingredient and dietary supplement manufacturers. This further reduces the likelihood that any company can demonstrate to FDA that they market an ODI. Again, we believe that FDA has created an unreasonable regulatory barrier preventing consumer access to safe dietary supplements.

Also consider that while the traditional oil refining process has not changed in over 60 years and is similar to all oil refining processes, to remove already low levels of contaminants, new steps have been introduced post-1994. Does FDA consider contaminant removal to result in a significant change in the chemical

composition of the dietary ingredient? If the answer is yes, then the FDA may be inadvertently creating an incentive for companies to avoid the burden of contaminant removal.

e) According to the Guidance, "FDA does not accept the inclusion of an ingredient on an industry list of pre-DSHEA dietary ingredients as proof that the ingredient is not a NDI." FDA's position and continued unwillingness to collaborate with industry has created an air of uncertainty of what is an ODI and further poses unreasonable regulatory barriers to the marketing of well recognized and safe dietary ingredients.

Once again, thank you for the opportunity to comment on this Guidance.

Sincerely,

Adam Ismail
Executive Director

Harry B. Rice, Ph.D.
Vice-President, Regulatory & Scientific Affairs

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