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VIA E-MAIL <http://www.fda.gov/dockets/ecomments>

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comment from JFI and JII on NDI Notification Program,
Docket No. 2004N--0454

To Whom It May Concern:

Patton Boggs LLP represents Jarrow Formulas, Inc. ("JFI"), which is a large Los Angeles-based company, founded in 1977, that develops, manufactures, markets, and sells dietary supplements. As such, JFI has submitted new dietary ingredient (NDI) Premarket Notifications in the past, and has an interest in the procedure by which a manufacturer or distributor of a new dietary supplement containing a new dietary ingredient is to submit information to FDA upon which it has based its conclusion that a supplement containing a new dietary ingredient will reasonably be expected to be safe. JFI does not currently have any NDI Notifications pending. This Comment is also written on behalf of Jarrow Industries, Inc. ("JII"), a manufacturing company in Santa Fe Springs, CA, also owned by Jarrow L. Rogovin, as is Jarrow Formulas, Inc.

On October 20, 2004, via a Federal Register notice, the Food and Drug Administration ("FDA" or "the Agency") solicited formal comments on FDA's premarket notification program for new dietary ingredients ("NDIs"), and on the content and evidence requirements for NDI notifications made under the Federal Food, Drug and Cosmetic Act ("the Act"). 69 Fed. Reg. 61680 (Oct. 20, 2004). As part of this call for Comments, the Agency presented a list of specific questions to elicit public and industry comment on particular NDI issues, presumably those that were of most concern in its analysis of its own NDI review process. JFI is pleased that the Agency has welcomed comment from the industry as to the type and quality of safety evidence to be submitted for an NDI Premarket Notification. However, JFI will not be responding to all of those several questions, but instead will focus on a few issues on which it has a strong position.

As a threshold matter, we observe that a new dietary ingredient is an ingredient (to be included in a new dietary supplement) that was not on the market in the U.S. as either a supplement or as a food before October 15, 1994. Section 8 of the Dietary Supplement Health

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and Education Act ("DSHEA"). However many such NDIs have been consumed as either foods, botanicals, or herbal tonics or remedies (or components of them) in other countries and cultures for centuries. Hence, the FDA must, by regulation, consider the "history of use" of an NDI as part of the Premarket Notification. 21 C.F.R. §190.6 (b)(4).

Accordingly, JFI offers the following Comments, in response to the Notice and call for comments, primarily on: further defining the proper standard of safety review; how the Agency can ensure that it is receiving the appropriate quality and quantity of scientific evidence based on this standard; and whether the Agency is, in practice, truly reviewing the safety information submitted in light of the standard required in Section 8 of the Dietary Supplement Health and Safety Act ("DSHEA"). In this Comment, JFI will discuss and analyze five points:

1. The standard for premarket review of new supplements containing new dietary ingredients, a reasonable expectation of safety—not a demonstrated certainty of safety—should continuously be kept in mind.

2. The safety standard for a new dietary ingredient should not be made to equate to or approach the safety standard for drugs.

3. The FDA should not publish general Guidelines for the safety evidence required for NDI Premarket Notifications, because—unlike for drug protocols—the safety testing and protocols for botanicals are case specific.

4. The FDA should consider allowing a lower standard or an abbreviated or expedited process for NDIs that are naturally-occurring constituents of foods and grandfathered dietary ingredients.

5. In the case of new dietary ingredients, the history of safe use from other countries should be given considerable weight in determining a reasonable expectation of safety, especially if those NDIs are components of foods routinely consumed in other countries.

I. The standard for safety of new dietary ingredients, "a reasonable expectation of safety," is much lower than the standard for an approved food additive or for GRAS status. The standard for GRAS ingredients, as is well-known, is a general recognition of a reasonable certainty of safety. In essence, the following two paragraphs from the FDA's proposed rule on GRAS substances published in the Federal Register on April 17, 1997, summarize the elements of a GRAS determination:

... a determination that a particular use of a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted. In contrast, a determination that a food additive is safe requires only technical evidence of safety.

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The common knowledge element of the GRAS standard includes two facets: (1) The data and information relied on to establish the technical element must be generally available; and (2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use. Neither facet is, by itself, sufficient to satisfy the common knowledge element of the GRAS standard.

(62 Fed. Reg. 18938, 18940; emphases added.) Another contrast between the safety evidence required for NDIs and that required for GRAS status is that while the GRAS standard requires that the information be "generally available," for an NDI Premarket Notification, foreign language articles on the substance's safety are acceptable, provided that an English language translation is also submitted to the Agency. What concerns JFI is that, in practice, the FDA in rejecting some NDI Notifications seems to be essentially requiring evidence of GRAS status or the same level of safety evidence that would be required for an FDA-approved food additive. This is simply not the standard for NDIs, nor are "grandfathered" dietary ingredients or existing dietary supplements on the market required to meet such a high standard of safety. Indeed, the very definition of dietary supplements in Section 3 of DSHEA exempts them from the GRAS requirement. Thus, the imposition of a GRAS standard—in practice—in the Agency's review of NDI Notifications, imposes a much higher standard of safety than for dietary supplements already on the market, some of which contain non-new dietary ingredients of dubious derivation, purity, and quality.

II. The safety standard for a new dietary ingredient should not be made to equate to or approach the safety standard for drugs. In the experience of JFI and that of other manufacturers and distributors known to JFI, often in response to an NDI Premarket Notification, the FDA requests, seeks, or seems to require 100-fold safety and toxicology studies. However, any requirement of a 100-fold study or LD-50 study to show the safety of a new dietary ingredient would have two problems: first, it imposes a higher standard than the reasonable expectation of safety required for new dietary supplements containing NDIs; and second, it superimposes a drug safety standard and protocol on a food supplement ingredient, and privileges a pharmaceutical review standard and approach—an analogy which is neither scientifically warranted or necessary, nor legally dictated, required or permitted.

Specifically, the toxicology studies and animal studies required for drug safety testing as the Phase I for drug approval, usually LD-50 tests and 100-fold studies, should not be required for NDIs. Instead, what is more appropriate are 5-fold or 10-fold tests. Rather than a drug model, for NDIs the manufacturer or distributor and the FDA should look to common food stuffs for guidance as to a reasonable standard of safety. Caffeine provides an excellent example. Coffee, tea and other sources of caffeine are ubiquitous in the American diet. A cup of coffee, depending on brewing, will usually supply 120 mg of caffeine, and a cup of tea, 50-60 mg of

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caffeine. This amount of caffeine seldom poses a problem for consumers, especially as individuals become habituated to the physiologic effects of caffeine. The generally-accepted opinion is that caffeine consumption warrants concern only when it reaches approximately 600 mg per day, that is, ten times the amount found in the morning cup of tea. In addition, methylxanthines caffeine at a dietary level of .5% fed to rats have been found to cause testicular problems.

In practice, a margin of safety of five-fold to ten-fold is quite typical of kitchen flavorings, herbs and spices, many of which have official GRAS status. Information from Dr. Siva Hari, Ph.D., President and CEO of Jarrow Industries, Inc. A person may safely consume a quarter teaspoonful of ground nutmeg, yet ingesting ten times this amount will prove to be toxic. Another example is that ingesting a quarter teaspoonful of table salt is safe, whereas consuming a tablespoonful at one time at the very least may cause nausea, and is not safe as a level of chronic intake—even over the course of one day. There have been studies of yet another common food, chocolate/cocoa, which now is recognized as a significant source of health-protecting antioxidants, and which is consumed by many individuals in quite large amounts. Yet when chocolate is consumed at 5% of the diet in laboratory animals, it clearly leads to some form of toxicity. See Tarka, S.M., Jr. et al. Chronic toxicity/carcinogenicity studies of cocoa powder in rats. Food Chem Toxicol 1991 Jan; 29(1): 7-19. Hershey Foods Corporation Technical Center, PA 17033-0805.

In light of the above, it appears reasonable that a five-fold to ten-fold safety margin (that is, the point at which serious rather than trivial side effects begin to appear) is quite reasonable in terms of everyday experience with foods that are not staples. Another consideration is that purchasers of dietary supplements will sometimes ingest two or three times the maximum amount recommended on labels, and responsible supplement manufacturers and distributors usually take this fact into account. A ten-fold safety margin is certainly sufficient in the light of normal consumer behavior. Such a margin of safety is already greater than that which is used for aspirin and quite a number of other OTC drug products. Information from Dr. S. Hari, Ph. D.

III. The FDA should not publish one general set of Guidelines for the safety evidence required for NDI Premarket Notifications. This is because the safety testing and protocols for botanicals are case specific, and any general guidelines based on drug testing protocols would be inapplicable and inappropriate. For example, phytochemicals and pharmaceuticals are very different; thus a drug testing model applied to new phytochemicals would not be a tenable argument. As shown above, LD-50 studies on food and herbal ingredients are not appropriate safety studies for dietary ingredients. Moreover, dietary supplements are consumed in a mode of providing long-term health-maintenance and disease-prevention benefits (in accordance with the Congressional findings of Section 2 of DSHEA), and are not intended for or taken for the cure or treatment of a disease. Thus, dietary supplements are used for their cumulative effect and not

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for a single-dose or short term effect. This is yet another reason why the usual animal studies and toxicology protocols used for drug testing are not applicable for an NDI Premarket Notification.

Thus, a more rational, science-based approach would be a flexible requirement that considered the many different extracts, constituents, and concentrations of constituents of a botanical or phytochemical NDI on a case-by-case basis. For example, in the next section JFI proposes that one particular category of NDI be reviewed through a different perspective, and that they be accorded a "favored treatment."

IV. The FDA should consider requiring fewer safety studies or an abbreviated process for constituents of foods and constituents of grandfathered dietary ingredients. JFI observes that many NDIs are not completely new and novel ingredients, not synthesized from a non-food or non-natural source material, and are not substances that have not (before October 15, 1994) been ingested by human beings in the U.S. Many of these naturally-derived NDIs are simply constituents of known foods or older dietary ingredients, e.g., the carotenoid lycopene which is a naturally-occurring constituent of tomatoes and other foods. JFI believes that there could be and should be a lower standard of evidence, and perhaps an abbreviated NDI review process for such known substances. Indeed, science and medicine are finding that many of these naturally-occurring constituents are essential to good health, e.g., lycopene being essential for prostate health. Thus, especially for NDIs that are food components, there should be a priority for FDA acceptance rather than an unreasonable bar to their inclusion in new dietary supplements—because of their future benefits to public health.

We start with Congress's definition of "dietary supplement" which also implies the same definition for "dietary ingredient":

The term "dietary supplement" means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E). 21 U.S.C. 321(ff)(1).

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Expanding on sub-section F above, a substance can meet the definition of dietary ingredient provided in 21 U.S.C. 321(ff)--provided that it is not tobacco, or a drug, antibiotic or biologic explicitly disallowed by 21 U.S.C. 321(ff)(3)(B)--if it is any of the following:

- An ingredient described in clause (A), (B), (C), (D), or (E) above. (a "DI")
- A concentrate of a DI;
- A metabolite of a DI;
- A constituent of a DI;
- An extract of a DI;
- A combination of DIs, or concentrates, metabolites, constituents, or extracts of DIs.

By analogy, JFI would like to suggest that if an NDI is simply a constituent or a metabolite or an extract (though not a concentrate) of a food consumed in another country or of a non-NDI, that is of a food or dietary supplement that was on the market in the U.S. before October 15, 1994 (hereafter collectively "DI"), that it be considered as having a threshold level of a reasonable expectation of safety, and that the manufacturer or distributor of a new supplement containing such a food-derived or naturally-derived NDI not be required to submit the same detailed safety evidence as for a truly novel ingredient. The reason for this is clear: If a substance is a metabolite or constituent of a DI, or an extract that is not a considerably higher strength or concentration as a naturally-occurring constituent of that DI, then there are inherent guarantees of safety from the consumption of the source food or grandfathered dietary ingredient. Common examples would be Sulphorophane glucosides (SGS) from broccoli, and lutein and zeaxanthine in spinach. Other examples of substances normally present in the body from dietary sources would be beta cryptoxanthin from tangerines, and zeaxanthine and lutein carotenoids from Marigold flower extract and maize (*Zea maize*).

Looking beyond food sources to the full scope of the natural world, other instances come to mind: silicon as orthosilicic acid, as found in mineral water, and particularly beer, and also present in ocean water (and which is essential to ocean life); and various enzymes such as nattokinase found in soy bean natto, as well as vitamin K2 also found in natto. In fact, an ironic example of this phenomenon is that folic acid is actually the non-natural, synthetic form of the nutrient, while foods contain 5-MTHF and related molecules. The same is true of vitamin B12. Cyanocobalamin is synthesized, while in nature methyl cyanocobalamin and related molecules are found. The point is that molecules found in food and those synthesized by living creatures, including humans, should be viewed favorably by the FDA in terms of their safety profiles, unless there is a reasonable basis for concern.

Arguably, new dietary supplements containing such food-based, naturally-occurring new constituents should be reviewed under a different standard. And one possible abbreviated and shortened review process might involve simply requiring affidavits from both the new food

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constituent ingredient manufacturer or marketer, and from an independent chemist, biochemist, or toxicologist that the subject "NDI" is simply a naturally-occurring constituent or metabolite of a known food or of an grandfathered botanical or other ingredient (or a non-concentrated extract of the same).

V. The history of safe use from other countries should be given considerable weight in determining a reasonable expectation of safety. Both established traditional use and widespread acceptance in another country with scientific standards comparable to those in the United States should be given great weight in coming to conclusions about reasonable expectations of safety for a new dietary ingredient. First, long term historic use by large numbers of individuals is itself a type of natural clinical trial which also has the value of lasting much longer and with much larger numbers of "subjects" than any formal, structured clinical trial can ever be maintained. For example, in Japan millions of people have been consuming soy for centuries. One of the major constituents of soy is isoflavones and two of the primary isoflavones in soy are genistin and daidzin (becoming genistein and daidzein in the body). There are several studies in Japan, including epidemiological studies, of the safety and health benefits of genistin and daidzin, because of their high concentrations in soy foods, especially in miso soup. Information from Dr. S. Hari, Ph. D. If genistin and daidzin were being offered as new dietary ingredients—in the same or lower concentrations as found in soy, and in the same or less daily amounts as are consumed with soy—then the extremely long and widespread (often daily) consumption of soy and miso in Japan would be highly indicative of the safety of these components.

In sum, all five of the reasons presented above are interrelated. Precisely because dietary supplements are not drugs, and NDIs are not drugs, drug safety standards, protocols, and analogies are not warranted or appropriate during an NDI Notification review. Precisely because the standard for NDIs is a reasonable expectation of safety of the resulting new supplement, and because constituents routinely consumed in foods (which are identical to the NDIs under consideration) offer in effect a long-term clinical trial on thousands or millions of people, a history of safe use in foods in other countries is very significant, and should be given greater weight by the Agency.

Thank you in advance for your serious consideration of these Comments.

Sincerely,

Susan D. Brienza

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On behalf of JFI and JII

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