IN THE UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF TEXAS

HOUSTON DIVISION

PAMELA GLOVER and CHARLES ELLIS, individually, and on behalf of all others similarly situated, Plaintiffs, vs. WOODBOLT DISTRIBUTION, LTD., a Texas limited liability company; and DOES 1-50, inclusive, Defendants.	Civil Action No. ***Jury Trial Requested***

PLAINTIFFS' CLASS ACTION COMPLAINT

INTRODUCTION

1. Defendant Woodbolt Distribution, Ltd. ("Woodbolt") is a company which manufactures, distributes, markets, and sells a variety of purported "muscle growth," "weight loss" and "protein" dietary supplements to consumers. Some of Woodbolt's best selling products are marketed under its "Cellucor" brand, including "C4 Extreme," "M5 Extreme," and "NO N-Zero Extreme" (collectively, the "Products"). These Products are purported dietary supplements which are marketed for use as "pre-workout" energy and muscle building supplements.

2. C4 Extreme is marketed as a "pre-workout" dietary supplement which provides benefits from "NO3 Pump Technology" and produces "Highly Explosive Energy." M5 Extreme is marketed as a "pre-workout" dietary supplement which produces "Explosive Energy Ignited by C4," "Muscle Pumps," "Strength & Size" and "Muscle Mass." However, C4 Extreme and M5 Extreme contain a dangerous stimulant that poses a serious health risk and has potentially life-threatening side effects. The stimulant, which is supposedly derived from the oil of the geranium plant, is known by many names, including "1, 3 dimethylamylamine," "methylhexanamine," and "geranamine" (hereinafter collectively referred to as "DMAA").

3. NO N-Zero Extreme is also marketed as a "pre-workout" dietary supplement which produces "Explosive Energy," "Muscle Pumps," "Strength & Definition" and "Muscle Protection." However, NO N-Zero Extreme contains an ingredient known by many names, including "Carbamyl-L-Glutamate," "Carglumic Acid," and "Carbaglu" (hereinafter referred to as "Carbaglu"). Carbaglu is actually an FDA-approved drug that is used for the treatment of a rare genetic disorder, Hyperammonemia, the use of which may have potentially serious adverse side effects.

4. Plaintiffs Pamela Glover and Charles Ellis (collectively "Plaintiffs") purchased Woodbolt's Products in reliance on the company's claims that the Products are safe, effective and legal dietary supplements, which the Products are not. At the time Plaintiffs purchased and used C4 Extreme and M5 Extreme, they were unaware that these Products contained a dangerous stimulant, DMAA, the use of which is banned by several athletic organizations, and sale of which is completely prohibited in certain countries. In addition, at the time Plaintiffs purchased and used NO N-Zero Extreme, they were unaware the Product contained an FDA-approved drug with potentially dangerous side effects.

5. DMAA was patented by Eli Lilly & Company in 1944 and later

marketed as a drug, beginning in 1971, under the trademark "Forthane" for use as a nasal decongestant and as a treatment for hypertrophied or hyperplasic oral tissues. DMAA is a vasoconstrictor and central nervous system stimulant which is on the World Anti-Doping Agency ("WADA") and Major League Baseball ("MLB") lists of banned substances. DMAA is totally banned in Canada and New Zealand. Recently, DMAA has gained popularity with young people as a designer drug used in "party pills."

6. Woodbolt fails to inform consumers that DMAA is a dangerous central nervous system stimulant which is banned by WADA, MLB, Canada and New Zealand, and that using the Products can cause consumers to test positive for an illegal substance and/or amphetamine use.

7. In addition, though DMAA is claimed to be an extract of geranium oil, most of the DMAA contained in products currently on the market is wholly "synthetic" DMAA, completely manufactured in laboratories, and is not derived from the geranium plant in any way whatsoever. In fact, Plaintiffs are informed and believe and on that basis allege that the DMAA in Woodbolt's Products is purely synthetic. Significantly, recent studies have also concluded that there is no DMAA in geranium oil at all, that DMAA cannot be extracted from geranium oil, and that all DMAA on the market is synthetic.

8. Furthermore, because DMAA was previously patented and marketed by Ely Lilly as a "drug" for the treatment of various medical conditions and disorders, it cannot now be considered a dietary ingredient which can be properly included in a dietary supplement.

9. Similarly, Carbaglu is a drug marketed by the Orphan Pharmaceutical Company. On March 18, 2010, Carbaglu was approved as a drug by the FDA for the treatment of a rare genetic disorder known as Hyperammonemia. This disorder is caused by the lack of a liver enzyme called N-acetylglutamate synthase, or "NAGS," and results in too much ammonia in the blood. Carbaglu acts by replacing

the NAGS enzyme and helps reduce the amount of ammonia in the blood. Carbaglu's side effects include infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headaches. (*See* Ex. 1, Drug information on Carbaglu.)

10. Nevertheless, the Products are falsely advertised by Woodbolt as safe, natural dietary supplements. Woodbolt fails to inform consumers that the Products do not meet the definition of a "dietary supplement," and that DMAA and Carbaglu do not meet the definition of a "dietary ingredient."

11. Recently, the United States Food and Drug Administration ("FDA") issued warnings about over-the-counter sales of various fraudulent and dangerous dietary supplements promoted mainly for bodybuilding, as is the case here. (*See* Ex. 2, "Tainted Products Marketed as Dietary Supplements;" *see also* Ex. 3, "Beware of Fraudulent Dietary Supplements.") The FDA notes that such products often "contain hidden or deceptively labeled ingredients," such as active ingredients contained in drugs required to be approved by the FDA prior to marketing, or other compounds that do not qualify as dietary ingredients. (Ex. 3, p. 1.)

12. Not content to deceptively market the Products as dietary supplements, Woodbolt goes a step further in its marketing scheme by making false, misleading, and unsubstantiated claims regarding the safety and effectiveness of the Products -- claims that Woodbolt knows are completely without merit or scientific substantiation -- in order to lure unsuspecting consumers into buying these so called "dietary supplements."

13. Accordingly, Plaintiffs bring this lawsuit, on behalf of themselves and a putative nation-wide class of purchasers of the Products, to enjoin Woodbolt and Does 1-50 (collectively "Defendants") from selling the Products without informing consumers that DMAA is a potentially dangerous, synthetic, banned stimulant, that Carbaglu is an FDA approved drug with potentially dangerous side effects, and from making illegal and deceptive marketing claims regarding the effectiveness and

safety of the Products. Plaintiffs further seek to recover restitution from Defendants in the amount of the total funds expended by Plaintiffs to purchase the Products, and by a class of all consumers who purchased the Products within four (4) prior to the filing of this Complaint through the present.

14. In the course of manufacturing, labeling, marketing, distributing, and selling the Products, Defendants, individually and acting as agents, employees, servants or alter egos of each other, have committed and continue to commit the above alleged illicit business practices in direct violation of Texas Deceptive Trade Practices Act ("DTPA") and warranty laws.

15. Furthermore, Defendants, individually and acting as agents, servants or employees of Woodbolt, have "misbranded" the Products as "dietary supplements."

THE PARTIES

16. Plaintiff Pamela Glover is a citizen of the state of California and a resident of Santa Clara County, California who purchased the Products in and around September, 2011 in Santa Clara County, California.

17. Plaintiff Charles Ellis is a citizen of the state of California and a resident of Alameda County, California who purchased the Products beginning in and around January, 2011 in Contra Costa County and/or Alameda County, California.

18. Plaintiffs are informed and believe that Woodbolt is a Texas limited liability company doing business in the state of California and throughout the United States. Woodbolt's principal place of business and headquarters are located at 715 North Main Street, Bryan, TX 77803.

19. Plaintiffs do not know the true names or capacities of the persons or entities sued herein as Does 1 through 50, inclusive, and therefore sues such Defendants by said fictitious names. Plaintiffs are informed and believe, and based thereon allege, that each of the Doe Defendants is in some manner legally responsible for the damages suffered by Plaintiffs and the members of the putative class as alleged herein. Plaintiffs will further amend this Complaint to set forth the

true names and capacities of these Defendants when they have been ascertained, along with appropriate charging allegations, as may be necessary.

20. Plaintiffs are informed and believe and thereon allege that at all times herein mentioned, there existed a unity of interest and ownership between and among the Defendants such that any individuality and separateness between and among them have ceased to exist such that each Defendant is the alter ego of each of the other Defendants, and they should not be allowed to evade justice by asserting the corporate or other limited liability veil.

21. Plaintiffs are informed and believe and based thereon allege that, at all times relevant herein, each of the Defendants was the agent, servant, employee, subsidiary, affiliate, partner, assignee, successor-in-interest, or representative of each of the other Defendants, and was acting in such capacity in doing the things herein alleged.

22. Plaintiffs are informed and believe that, at all relevant times, Defendants were, and still are, aware, or should have been aware, that DMAA is a potentially dangerous, synthetic stimulant banned by several athletic organizations and in certain countries, that Carbaglu is an FDA approved drug, that use of the Products may have serious and medically risky adverse side effects, and that use of the Products does not produce the results promised on the label and/or cannot produce the promised results without serious adverse side effects. Nevertheless, Defendants market the Products as safe and effective dietary supplements, and fail to inform consumers of the true facts.

23. In committing the wrongful acts alleged herein, Defendants planned and directly participated in and furthered a common scheme by means of false, misleading and deceptive advertising and labeling representations to induce consumers to purchase the Products.

24. Defendants aided and abetted and knowingly assisted each other in their wrongful conduct as herein alleged.

JURISDICTION AND VENUE

25. This Court has subject matter jurisdiction over this class action pursuant to 28 U.S.C. § 1332 and the Class Action Fairness Act ("CAFA"). Plaintiffs and other members of the putative nationwide class are citizens of the United States. Defendant Woodbolt is a Texas limited liability company with its principal place of business in the state of Texas. Plaintiffs are informed and believe, and based thereon allege, that more than two thirds of members of the putative nationwide class are citizens of a state different than Defendants'. Plaintiffs are also informed and believe, and based thereon allege, the amount in controversy in this case, exclusive of interests and costs, exceeds $5,000,000.00 and the total number of putative nationwide class members is, at a minimum, in the thousands, if not hundreds of thousands.

26. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(a)(1), (a)(2), and (a)(3) and § 1391(c) in that a substantial part of the events or omissions giving rise to the claims asserted in this action occurred in this judicial district, and Defendants reside in this judicial district, do substantial business in this judicial district, have received substantial benefit from doing business in this judicial district, and have knowingly engaged in activities directed at consumers in this judicial district. Furthermore, a significant number of Defendants' customers are Texas residents, and the wrongful acts alleged herein have affected members of the class throughout Texas. Texas has a significant contact or aggregation of contacts to the claims at issue herein in that Defendants promote, market and sell the Products in Texas. Defendants are subject to personal jurisdiction anywhere in the state of Texas, including in this judicial district.

27. Each of the Defendants, individually and acting as agents, servants, officers, directors, employees, managers, controlling principals, shareholders and/or alter egos of Woodbolt, are headquartered and do business in Texas, have sufficient minimum contacts with Texas, and/or otherwise intentionally avail themselves of

the markets in Texas through the promotion, marketing and sale in Texas of the Products, to render the exercise of jurisdiction by this Court permissible under traditional notions of fair play and substantial justice. In addition, the business activities of Defendants at issue in this Complaint were within the flow of and substantially affected interstate trade and commerce. There has been a continuous and uninterrupted flow of activities in interstate commerce throughout the class period.

FACTS COMMON TO ALL CAUSES OF ACTION

28. Although Defendants have been extremely successful with the marketing, sale and distribution of the Products, their success has been based on false, misleading and deceptive advertising. Woodbolt sells the Products through a deceptive marketing campaign claiming that the Products are safe dietary supplements which if used by a consumer before a workout will provide an energy boost which will result in increased muscle mass. Specifically, Woodbolt advertises: that C4 Extreme produces "Highly Explosive Energy," and has "NO3 Pump Technology" (*see* Ex. 4, labeling for C4 Extreme); that M5 Extreme produces "Explosive Energy Ignited by C4" which increases "Muscle Pumps," "Strength & Size" and "Muscle Mass" (*see* Ex. 5, labeling for M5 Extreme); and that NO N-Zero Extreme produces "Explosive Energy" resulting in increased "Muscle Pumps," "Strength & Definition" and "Muscle Protection" (*see* Ex. 6, labeling for NO N-Zero Extreme).

29. Recent studies have shown that DMAA is not a natural constituent of the geranium plant, and that all DMAA is synthetic. *See* Ex. 8 (excerpt from Interview with Ed Wyszumiala of NSF International); Ex. 9 ("AHPA: Review of Research Shows DMAA Not Naturally From Geranium"). In fact, NSF International, a world leader in standards development and product certification for over 65 years, and widely recognized for its scientific and technical expertise in product certification, has publicly stated that it has tested geranium oil down to a parts per billion screen,

and DMAA is not derived from natural geranium oil; it is a synthetic compound and not a natural constituent of the botanical geranium. Furthermore, experts in the industry have been extremely concerned that this potent stimulant drug will lead to serious health issues and even death, as was the case with ephedra before it was banned by the FDA in 2003. *See* Ex. 10 ("Synthetic Geranium Still Raising Industry Red Flags").

30. The labeling for C4 Extreme claims that consumption of the Product produces "Highly Explosive Energy." (*See* Ex. 4.) The labeling for M5 Extreme claims the Product will produce "Explosive Energy Ignited By C4," and increase "Muscle Pumps," "Strength & Size" and "Muscle Mass." (*See* Ex. 5.) The labeling for NO N-Zero Extreme claims the Product will produce "Explosive Energy," increase "Muscle Pumps" and "Strength & Definition," and provide "Muscle Protection." (*See* Ex. 6.)

31. All of the Products advertise that they will result in the consumer experiencing benefits from, *inter alia*, a "muscle pump." In bodybuilding building, a "muscle pump" is a desired physiological effect which results from intense physical exercise that is essentially a tight, blood-congested feeling in a muscle after it has been intensely trained. It is caused by a rapid influx of blood into the muscle to remove toxins (such as lactic acid and carbon dioxide) and replace such toxins with nutrients and oxygen. The Products advertise that consumer will experience increased energy, increased muscle strength, increased muscle mass, and/or increased muscle definition.

32. Moreover, as noted previously, DMAA was patented in 1944 by Eli Lilly and Company (U.S. Patent #2,350,318) and marketed for sale as a drug under the brand name Forthane for the relief of nasal congestion. *See* Ex. 11 (Patent for DMAA); Ex. 12 (Trademark information regarding Forthane); Ex. 13 (Advertisements by Eli Lilly for the drug Forthane). DMAA has also been used in combination with other drugs as a treatment for hypertrophied or hyperplastic oral

tissues. *See* Ex. 14 (Patent utilizing DMAA to treat hypertrophied gums).

33. Plaintiffs are informed and believe that the use of DMAA can have extremely dangerous side effects. Significantly, Don Caitlin, preeminent anti-doping scientist, has noted in a Washington Post news article that DMAA has a chemical structure similar to amphetamine and ephedrine, and can cause increases in heart rate and blood pressure, and even death. Caitlin further stated "this substance should not be out there…it's a dangerous material." *See* Ex. 15 (Washington Post Article entitled "Chemist's New Product Contains Hidden Substance"). The safety concerns associated with DMAA have been well-documented, including concerns that DMAA is a dangerous and addictive substance that can cause headache, nausea and stroke. *See* Ex. 16 (excerpt from article entitled "Jack3d and other MHA-containing Supplements Fuel Adulteration, Safety Concerns"). To make things worse, DMAA is widely used as a "designer drug" in dangerous "party pills." *See* Ex. 17 (excerpt from article entitled "New pill ingredient worries ministry").

34. Despite Defendants' knowledge of the dangers associated with DMAA use, they continue to advertise and sell the Products to unknowing consumers as safe, natural dietary supplements. Defendants have failed to warn consumers that DMAA use can potentially cause serious adverse side effects, that DMAA is considered to be a potentially dangerous, performance-enhancing stimulant in the sports world and, as such, is classified as a banned substance by MLB, WADA and the United States Anti-Doping Agency ("USADA"). *See, e.g.*, Ex. 18 (WADA 2011 Prohibited Substances List). Numerous athletes in various sports throughout the world have been suspended or disqualified for unknowingly using products containing DMAA. However, despite having knowledge of these facts, Defendants have never specifically warned consumers that DMAA is actually banned by certain sports organizations, as well as being completely banned in Canada and New Zealand, and could cause users to fail drug tests.

35. Carbaglu is a drug originally developed by the Orphan Pharmaceutical

Company, receiving European marketing authorization in 2003 and approved by the FDA on March 18, 2010, for the treatment of Hyperammonemia, a rare genetic disorder. Defendants, however, wrongfully market NO N-Zero Extreme as a safe, over-the-counter dietary supplement despite the fact that the product label lists a drug, Carbaglu, as one of its primary ingredients. *See* Ex. 6.

36. Plaintiffs are informed and believes that the use of Carbaglu can have extremely dangerous side effects, including infections, vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache. (*See* Ex. 1.)

37. Despite Defendants' knowledge of the dangers associated with Carbaglu use, they continue to advertise and sell NO N-Zero Extreme to unknowing consumers as a safe, natural dietary supplement. Defendants have failed to warn consumers that Carbaglu is a drug, use of which can potentially cause serious adverse side effects.

38. Defendants not only promise consumers that the Products are safe, they also assure consumers the Products are effective and can produce amazing results. Defendants promise these results knowing that none of the Products, nor any of the Products' individual ingredients at the levels contained therein, can produce these promised results. Plaintiffs are informed and believe, and on that basis allege, that any existing efficacy studies are on individual ingredients contained within the Products, and none of these studies are on healthy humans with equivalent dosing or routes of administration. Therefore, such claims are purely false advertising to induce consumers to spend their hard earned money on unproven Products solely for the Defendants' monetary gain.

39. Following the DMAA-linked deaths of two soldiers from heart attack in 2011, and after recording a number of other serious adverse health effects suffered by known and potential users of products containing DMAA, including kidney and liver failure, seizures, loss of consciousness, heat injury and muscle breakdown

during exertion, and rapid heartbeat, the Army launched a safety investigation of the substance. As a result, on December 3, 2011, all bodybuilding and weight loss supplements containing DMAA were pulled from the shelves of all Army, Air Force and Navy Exchange Service stores around the world. *See* Ex. 19 (Article from Stars and Stripes entitled "Army probing connection between body building supplement, 2 deaths," dated December 15, 2011.)

40. On April 27, 2012, the FDA published a news release stating that the agency had issued warning letters to ten manufacturers and distributors of dietary supplements, containing DMAA, for the companies' failure to provide the FDA with evidence of the safety of their products. *See* Ex. 20 (FDA News Release titled "FDA Challenges Marketing of DMAA Products for Lack of Safety Evidence"). The FDA warning letters advised the companies that the agency is not aware of evidence or history of use to indicate that DMAA is safe. The FDA also warned the companies that synthetically-produced DMAA is not a "dietary ingredient" and, therefore, is ineligible to be used as an active ingredient in a dietary supplement. *See. e.g.*, Ex. 21 (FDA DMAA Warning Letter to Nutrex Research, Inc. dated April 24, 2012.)

41. Despite knowing C4 Extreme and M5 Extreme contain DMAA, a synthetic, banned and potentially dangerous stimulant, that NO N-Zero Extreme contains Carbaglu, an FDA approved drug with potentially dangerous side effects, and that the Products are ineffective for their intended use, Defendants continue to, among other things:

(a) Fail to warn consumers about the extreme health dangers and potential side effects of the Products;

(b) Knowingly withhold from consumers material information regarding the DMAA contained in the C4 Extreme and M5 Extreme, including but not limited to the fact that DMAA is banned by WADA, USADA and MLB, and banned completely

in Canada and New Zealand;

(c) Knowingly withhold from consumers material information regarding the Carbaglu contained in NO N-Zero Extreme, including but not limited to the fact that Carbaglu is an FDA approved drug; and,

(f) Falsely advertise the Products as having specific muscle-building properties that the Products do not have.

42. The labeling for the Products displays the disclaimer that the statements made on the labeling "have not been evaluated by the Food and Drug Administration." In this action, Plaintiffs do not sue to subject Defendants to the FDA pre-market approval or post-market regulatory processes, but rather, to stop the false, deceptive, and often illegal labeling and advertising of the Products under Texas law as described herein.

PLAINTIFFS' EXPERIENCES WITH THE PRODUCTS

43. In and around September of 2011, Plaintiff Pamela Glover purchased C4 Extreme, M5 Extreme, and NO N-Zero Extreme from a GNC store in Santa Clara County, California. Prior to purchasing these three Products, Plaintiff Glover reviewed the product packaging and read the labeling statements which claim, among other things, that: (1) each of the Products is a "dietary supplement;" (2) C4 Extreme will produce "Highly Explosive Energy" and has "NO3 Pump Technology;" (3) M5 Extreme will produce "Explosive Energy Ignited By C4," "Muscle Pumps," "Strength & Size" and "Muscle Mass;" and, (4) NO N-Zero Extreme will produce "Explosive Energy," "Muscle Pumps," "Strength & Definition," and "Muscle Protection."

44. At the time Plaintiff Glover purchased C4 Extreme and M5 Extreme, she was not aware, and the Product packaging did not inform her, that: (1) DMAA is a potentially dangerous, synthetic stimulant banned by WADA, USADA and MLB; (2) DMAA is banned totally in Canada and New Zealand; (3) DMAA was once

marketed as the drug Forthane; (4) using DMAA can cause serious side effects; (5) the labeling for C4 Extreme and M5 Extreme makes claims without adequate scientific substantiation or adequate labeling explanation; and (6) using DMAA could cause her to test positive for a banned substance or for use of amphetamines.

45. Similarly, at the time Plaintiff Glover purchased NO N-Zero Extreme, she was not aware, and the Product packaging did not inform her, that: (1) Carbaglu is an FDA approved drug used for the treatment of Hyperammonemia; (2) use of Products containing Carbaglu can cause serious side effects; and (3) the labeling for NO N-Zero Extreme makes claims without adequate scientific substantiation or adequate labeling explanation.

46. Plaintiff Glover used the Products without knowing any of the aforementioned facts. In purchasing the Products, Plaintiff Glover relied on the representations made by Defendants on the labeling and packaging for the Products. Plaintiff Glover reasonably believed and relied on Defendants' representations that the Products are safe and effective dietary supplements which can be legally sold over-the-counter. Plaintiff Glover used the Products in accordance with the labeling instructions. She used the Products as directed for weeks, but did not experience "Highly Explosive Energy," "Muscle Pumps," "Strength & Size," "Strength & Definition," "Muscle Mass," or "Muscle Protection." However, Plaintiff Glover did experience severe adverse side effects, including feeling jittery and anxious and having persistent headaches. Given these serious side effects, the Products did not work for Plaintiff Glover as she expected, nor as promised by Defendants' labeling representations.

47. Furthermore, Plaintiff Glover would have never purchased or used the Products had she known the Products are not safe, natural and effective dietary supplements as they are advertised to be, but in fact are ineffective and contain DMAA, a banned and extremely dangerous synthetic pharmaceutical substance, or Carbaglu, an FDA approved drug used for the treatment of Hyperammonemia.

Plaintiff Glover has suffered injury in the amount of money she spent to purchase the Products.

48. In or around January, 2011, Plaintiff Charles Ellis purchased one 390g container of C4 Extreme from a local GNC store in Contra Costa County. In or around March 2011, Plaintiff Ellis purchased one 712g container of M5 Extreme from the same GNC store. In or around May 2011, Plaintiff Ellis purchased one 277g container of NO N-Zero Extreme from a local GNC store. Prior to purchasing these three Products, Plaintiff Ellis reviewed the product packaging and read the labeling statements which claim that: (1) each of the Products is a "dietary supplement;" (2) C4 Extreme will produce "Highly Explosive Energy" and has "NO3 Pump Technology;" (3) M5 Extreme will produce "Explosive Energy Ignited By C4," "Muscle Pumps," "Strength & Size" and "Muscle Mass;" and, (4) NO N-Zero Extreme will produce "Explosive Energy," "Muscle Pumps," "Strength & Definition," and "Muscle Protection."

49. At the time Plaintiff Ellis purchased C4 Extreme and M5 Extreme, he was not aware, and the Product packaging did not inform him, that: (1) DMAA is a potentially dangerous, synthetic stimulant banned by WADA, USADA and MLB; (2) DMAA is banned totally in Canada and New Zealand; (3) DMAA was once marketed as the drug Forthane; (4) using DMAA can cause serious side effects; (5) the labeling for C4 Extreme and M5 Extreme makes claims without adequate scientific substantiation or adequate labeling explanation; and (6) using DMAA could cause him to test positive for a banned substance or for use of amphetamines.

50. Similarly, at the time Plaintiff Ellis purchased NO N-Zero Extreme, he was not aware, and the Product packaging did not inform him, that: (1) Carbaglu is an FDA approved drug used for the treatment of Hyperammonemia; (2) use of Products containing Carbaglu can cause serious side effects; and (3) the labeling for NO N-Zero Extreme makes claims without adequate scientific substantiation or adequate labeling explanation. Plaintiff Ellis used the Products without knowing

any of the aforementioned facts.

51. In purchasing the Products, Plaintiff Ellis relied on the representations made by Defendants on the labeling and packaging for the Products. Plaintiff Elis reasonably believed and relied on Defendants' representations that the Products are safe and effective dietary supplements which can be legally sold over-the-counter. Plaintiff Ellis used the Products in accordance with the labeling instructions. He used the Products as directed for approximately five (5) months but did not experience the promised "Highly Explosive Energy," "Muscle Pumps," "Strength & Size," "Strength & Definition," "Muscle Mass," or "Muscle Protection." However, Plaintiff Ellis did experience severe adverse side effects, including extreme anxiety, persistent cold and flu symptoms, and nausea. Given these serious side effects, the Products did not work for Plaintiff Ellis as he expected, nor as promised by Defendants' labeling representations.

52. Furthermore, Plaintiff Ellis would have never purchased or used the Products had he known the Products are not safe, natural and effective dietary supplements as they are advertised to be, but in fact are ineffective and contain DMAA, a banned and extremely dangerous synthetic stimulant, or Carbaglu, an FDA approved drug used for the treatment of Hyperammonemia. Plaintiff Ellis has suffered injury in the amount of the money he spent to purchase the Products.

CLASS ACTION ALLEGATIONS

53. Plaintiffs bring this class action for injunctive relief, restitution and other equitable and monetary relief on behalf of the putative class (the "Class") consisting of:

> **All persons residing in the United States who purchased the Products for personal use within four years prior to the date the Complaint in this action was filed through the present (the "Class Period").**

54. Excluded from the Class are governmental entities, Defendants, any entity in which Defendants have a controlling interest, and Defendants' officers,

directors, affiliates, legal representatives, employees, co-conspirators, successors, subsidiaries, and assigns. Also excluded from the Class are any judge, justice, or judicial officer presiding over this matter and the members of their immediate families and judicial staff.

55. The proposed Class is so numerous that individual joinder of all its members is impracticable. Due to the nature of the trade and commerce involved, however, Plaintiffs believe that the total number of Class members is, at a minimum, in the hundreds. While the exact number and identities of the Class members are unknown at this time, such information can be ascertained through appropriate investigation and discovery. The disposition of the claims of the Class members in a single class action will provide substantial benefits to all parties and to the Court.

56. There is a well-defined community of interest in the questions of law and fact underlying the claims of each member of the Class, and these common questions predominate over any questions that may affect individual Class members. The Common questions of fact and law include, but are not limited to, the following:

(a) Whether Defendants fail to disclose to consumers that DMAA is a potentially dangerous stimulant which is banned by several sports organizations, including MLB, WADA and USADA, and completely banned in Canada and New Zealand;

(b) Whether Defendants fail to disclose to consumers the potential adverse side effects associated with using Products containing DMAA and Carbaglu;

(c) Whether Defendants fail to disclose to consumers the potential adverse side effects associated with using Products containing Carbaglu;

(d) Whether Defendants fail to disclose to consumers that DMAA was previously sold as the drug Forthane;

(e) Whether Defendants fail to disclose to consumers that Carbaglu is an FDA approved drug used for the treatment of Hyperammonemia;

(f) Whether Defendants fail to disclose to consumers that the labeling for the Products contains structure/function claims which are not adequately explained and for which Defendants do not have adequate scientific substantiation;

(g) Whether Defendants make false, misleading, deceptive and/or illegal safety and efficacy omissions and representations on the Product labeling;

(h) Whether the Product claims and omissions herein alleged are false, misleading, deceptive, illegal, material and/or reasonably likely to deceive consumers;

(i) Whether Defendants' conduct is fraudulent and/or violates public policy;

(j) Whether Defendants have engaged in unfair, unlawful and/or fraudulent business practices in labeling, advertising, marketing and distributing the Products;

(k) Whether Defendants engaged in conduct in violation of the DTPA;

(l) Whether Defendants knowingly concealed material facts for the purpose of inducing unwary consumers into spending money on the Products;

(m) Whether Defendants' representations, concealments and non-disclosures concerning the Products are likely to deceive consumers;

(n) Whether Defendants' labeling for the Products is false, misleading, illegal and/or deceptive;

(o) Whether Defendant represent that the Products have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities which they do not have, in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(5);

(p) Whether Defendants knew or should have known that the Products do not have the sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities for which Defendants advertised and/or labeled the Products;

(q) Whether Defendants represent that the Products are of a particular standard, quality, or grade, or that goods are of a particular style or model, if they are of another, in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(7);

(r) Whether Defendants knew or should have known that the Products are of a particular standard, quality, or grade, or that goods are of a particular style or model, when in fact, they are of another;

(s) Whether Defendants advertise the Products with intent not to sell them as advertised, in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(9);

(t) Whether Defendants continued to sell the Products after knowing the preceding facts;

(u) Whether Defendants breached express and implied warranties as a result of their misrepresentations in selling the Products;

(v) Whether Defendants have been unjustly enriched;

(w) The nature and extent of damages and other remedies to which the conduct of Defendants entitle the members of the Class, and/or which should be assessed against Defendants.

(x) Whether Plaintiffs and the Class are entitled to injunctive relief; and,

(y) Whether Plaintiffs and the Class are entitled to restitution.

57. Plaintiffs' claims are typical of the claims of the members of the Class. Plaintiffs and all members of the Class have been similarly affected by Defendants' common course of conduct since they were exposed to the omissions and misrepresentations in the labeling for the Products, and those omissions and misrepresentations were material to their decision to purchase the Products.

58. Plaintiffs will fairly and adequately represent and protect the interests of the Class in that they are typical purchasers of the Products. Plaintiffs have retained counsel with substantial experience in handling complex class action litigation. Plaintiffs and their counsel are committed to vigorously prosecuting this action on behalf of the Class. Plaintiffs have retained a firm which is widely recognized as among the most successful and effective class action litigation firms in California.

59. Plaintiffs and the members of the Class have suffered, and will continue to suffer, harm as a result of Defendants' unlawful and wrongful conduct. A class action is superior to other available methods for the fair and efficient adjudication of the present controversy. Individual joinder of all members of the class is impracticable. Even if individual Class members had the resources to pursue individual litigation, it would be unduly burdensome to the courts in which the individual litigation would proceed. Individual litigation magnifies the delay and expense to all parties and the court system to resolve the controversies engendered by Defendants' common course of conduct. The class action device allows a single court to provide the benefits of unitary adjudication, judicial economy, and the fair and efficient handling of all Class members' claims in a single forum. The conduct of this action as a class action conserves the resources of the parties and of the judicial system and protects the rights of the Class members. Furthermore, for many, if not most, a class action is the only feasible mechanism that allows an

opportunity for legal redress and justice.

60. Adjudication of individual Class members' claims with respect to the Defendants would, as a practical matter, be dispositive of the interests of other Class members not parties to the adjudication, and could substantially impair or impede the ability of other class members to protect their interests

CLAIMS FOR RELIEF

FIRST CLAIM FOR RELIEF

VIOLATION OF TEXAS DECEPTIVE TRADE PRACTICES ACT

(Texas Bus. & Comm. Code §§ 17.41 though 17.63)

61. Plaintiffs incorporate by reference all the above allegations as if fully set forth herein.

62. The Products are "goods" within the meaning of Tex. Bus. & Comm. Code § 17.45(1).

63. Defendants are "persons" within the meaning of Tex. Bus. & Comm. Code § 17.45(3).

64. Putative class members are "consumers" within the meaning of Tex. Bus. & Comm. Code § 17.45(4).

65. Plaintiff's and each and every class member's purchases of the Products constitute trade and commerce within the meaning of Tex. Bus. & Comm. Code § 17.45(6).

66. The policies, acts, and practices heretofore described were intended to result in the sale of the Products to the consuming public, particularly consumers seeking increased energy for workouts and to rapidly build muscle mass and strength.

67. These actions violated, and continue to violate, the DTPA in the following ways:

a. Failing to disclose material facts concerning the Products to the

consuming public.

b. representing that the Products have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities which they do not have, in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(5).

c. representing that the Products are of a particular standard, quality, or grade, or that goods are of a particular style or model, if they are of another, in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(7).

d. advertising the Products with intent not to sell them as advertised, in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(9).

68. Despite of its superior knowledge and awareness of the true facts concerning the efficacy and safety of the Products and of DMAA, Defendants intentionally withheld, and continues to withhold, such knowledge from putative class members to boost business profits and/or to reap unconscionable unjust enrichment to itself. This conduct was and is willful, malicious and oppressive, and in conscious disregard of the rights of Plaintiffs and the Class.

69. Defendants intentionally engaged in this conduct.

70. Prior to the filing of this action, Plaintiffs purchased the Products for their personal use. In so doing, they reviewed, believed, and relied upon the marketing omissions and claims on the Product packaging. The Plaintiffs consumed the Products as directed, but the Products did not work as advertised. Plaintiffs never would have purchased the Products had they known that the advertised benefits were completely fictitious and that the Products contain a synthetic, dangerous, and banned stimulant, or an FDA approved drug used for the treatment of Hyperammonemia. Unaware of these facts, Plaintiffs purchased the Products and consumed the Products as directed, but they did not experience the advertised benefits. Moreover, they experienced serious and severe side effects from use of the Products.

71. Defendants' practices, omissions, acts and course of conduct in connection with their promotion and sale of the Products, as described hereinabove, are likely to mislead a reasonable consumer acting reasonably under the circumstances to his or her detriment. Like Plaintiffs, members of the putative Class would not have purchased the Products if Defendants had disclosed the truth and all facts concerning the Products..

72. Plaintiffs and members of the putative Class have been directly and proximately injured by the conduct of Defendants, and such injury includes payment for the Products.

73. Defendants' wrongful business practices constituted, and constitute, a continuing course of conduct in violation of the DTPA since Defendants are still falsely representing that the Products have characteristics, benefits and uses which they do not have, continue to fail to disclose the true characteristics and qualities of the Products, and thereby have injured and continue to injure Plaintiffs and the putative Class.

74. As a direct and proximate result of Defendants' violations of law, Plaintiffs and the Putative Class have been injured. Prior to filing suit, Plaintiffs' counsel mailed to Defendants, by certified mail, return receipt requested, written notice on behalf of both Plaintiff Pamela Glover and Plaintiff Charles Ellis, as required by Tex. Bus. & Comm Code § 17.505. The Notice demanded that within sixty (60) days from receipt, Defendants, *inter alia*, adequately correct, repair, replace or otherwise rectify the deceptive practices described in this Complaint for the entire Class, pursuant to Tex. Bus. & Comm. Code § 17.505. The Notice further demanded that Defendants provide notice and full compensation to consumers who have purchased the Products. Defendants did not respond to Plaintiffs' notice and demand letter, and failed to meet Plaintiffs' demands.

75. Plaintiffs and the Class seek an order of this Court enjoining Defendants from continuing to engage in unlawful, unfair, or deceptive business practices and

any other omission or act prohibited by law, including those set forth in this Complaint. Plaintiffs and the Class also seek an order: (i) enjoining Defendants from failing and refusing to make full restitution of all moneys wrongfully obtained as a result of their violations of the DTPA; (ii) compelling Defendants to disgorge all ill-gotten revenues and/or profits earned or retained as a result of their violations of the DTPA; and (iii) for attorneys' fees and costs.

SECOND CLAIM FOR RELIEF

BREACH OF IMPLIED WARRANTY

(Tex. Bus. & Comm. Code §§ 2.314-2.315)

76. Plaintiffs incorporate by reference all the above allegations as if fully set forth herein.

77. The Products were sold with the implied warranty of merchantability in that the Products would pass without objection in the trade, are fit for the ordinary purpose for which they are sold and used, are adequately contained, packaged, and labeled, and conform to the promises or affirmations of fact made on the packaging and labeling. Defendants' Products do not meet the foregoing criteria.

78. The defects in the Products existed prior to the delivery of the Products to Plaintiffs and putative Class members. Plaintiffs provided Defendants with notice of their warranty claims, on behalf of themselves and putative Class members, by virtue of notice letters sent to Defendants on March 1, 2012. Defendants have failed to fulfill their warranty obligations despite said notices. Plaintiffs and putative Class members have incurred damages as described herein as a direct and proximate result of the defective Products and Defendants' breach of the implied warranty of merchantability, in that Plaintiffs and the putative Class have paid the purchase price for the defective Products. Plaintiffs, on behalf of themselves and putative Class members, have requested that Defendants correct the defects and Defendants have failed to do so. Plaintiffs and putative Class members are entitled to refund of the purchase price paid for the Products, consequential and incidental damages, costs

and expenses, including attorney's fees.

THIRD CLAIM FOR RELIEF

BREACH OF EXPRESS WARRANTY

(Tex. Bus. & Comm. Code § 2.313)

79. Plaintiffs incorporate by reference all the above allegations as if fully set forth herein.

80. The Products were sold with an express warranty, as Defendants made express affirmations of fact and promises that the Products are dietary supplements containing proper dietary ingredients, and regarding the nature, safety and efficacy of the Products.

81. The Products were sold with an express warranty because Defendants' descriptions of the Products on the labeling and packaging were intended to become part of the basis of the bargain. The Products are not suitable for the purpose for which they were required and sold as the Products are not in fact safe and effective, and do not fall within the definition of a "dietary supplement."

82. The defects in the Products existed prior to the delivery of the Products to Plaintiffs and the putative Class members.

83. Plaintiffs, on behalf of themselves and putative Class members, provided Defendants with notice of their warranty claims by virtue of the letter sent to Defendants. Defendants failed to fulfill their warranty obligations despite said notice.

84. Plaintiffs and putative Class members have incurred damages as described herein as a direct and proximate result of the defective Products and Defendants' breach of the express warranties, in that Plaintiffs and members of the putative Class have paid the purchase price for the defective Products. Plaintiffs, on behalf of themselves and putative Class members, requested that Defendants correct the defect and refund amounts paid for the defective Products, and Defendants have failed to do so. Plaintiffs and putative Class members are entitled to refund of the

purchase price of the Products, consequential and incidental damages, and costs and expenses, including attorney's fees.

FOURTH CLAIM FOR RELIEF
UNJUST ENRICHMENT/RESTITUTION

85. Plaintiffs incorporate by reference all of the above allegations as if fully set forth herein.

86. This cause of action is being asserted on behalf of Plaintiffs and putative Class members who purchased Products within the applicable statute of limitations period.

87. Defendants have benefited from, and have been unjustly enriched by, their wrongful conduct as alleged hereinabove. Defendants sold the Products to Plaintiffs and members of the putative Class based upon deceptive conduct, omissions and misrepresentations as to uses and qualities which the Products do not possess, and which Defendants were, and still are, aware the Products do not possess.

88. Defendants have knowledge of this benefit, and have voluntarily accepted and retained this benefit.

89. The circumstances as described herein are such that it would be inequitable for Defendants to retain these ill-gotten benefits without paying the value thereof to Plaintiffs and putative Class members.

90. Plaintiffs and putative Class members are entitled to restitutionary disgorgement of the amount of Defendants' ill-gotten gains, including interest, resulting from Defendants' unlawful, unjust and inequitable conduct as described above.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs, on behalf of themselves and all other persons

similarly situated, pray for judgment against Defendants, as follows:

1. An Order certifying the proposed Class as defined hereinabove, and any appropriate sub-class(es) thereof, and appointing Plaintiffs and their attorneys to represent the certified Class, with notice thereto to be paid by Defendants;

2. An award of general damages according to proof;

3. An award of special damages according to proof;

4. An award of restitution in an amount according to proof;

5. Restitutionary disgorgement in an amount according to proof;

6. For a temporary restraining order, a preliminary injunction, and a permanent injunction enjoining Defendants, and their agents, servants, employees and all persons acting under or in concert with them, to cease and desist from the following acts:

(a) Selling, marketing or advertising C4 Extreme and M5 Extreme without disclosing to consumers that DMAA is a dangerous, synthetic stimulant, the use of which could potentially have serious adverse side effects;

(b) Selling, marketing or advertising NO N-Zero Extreme without disclosing to consumers that Carbaglu is a drug approved by the FDA for use as a treatment for Hyperammonemia, the use of which could potentially have serious adverse side effects;

(c) Selling, marketing or advertising C4 Extreme and M5 Extreme without disclosing to consumers that DMAA is banned by certain athletic organizations and in certain countries;

(d) Selling, marketing or advertising NO N-Zero Extreme without disclosing to consumers that Carbaglu does not fall within the definition of a “dietary ingredient,” and NO N-Zero Extreme does not fall within the definition of a “dietary supplement;”

(e) Selling, marketing or advertising C4 Extreme and M5 Extreme without disclosing to consumers that DMAA was previously marketed as the drug Forthane;

(f) Selling, marketing or advertising the Products without disclosing to consumers that Defendants do not have adequate scientific substantiation for the structure/function claims made on the Product labeling;

(g) Selling, marketing or advertising the Products without adequately explaining the structure/function claims made on Product labeling, and the effect of each nutrient and/or ingredient contained in the Products on the structure or function of the human body;

(h) Selling, marketing or advertising the Products with any representation or suggestion that consumption of the Products will safely and effectively generate energy or enhance physical exercise, increase muscle mass, strength or definition, or provide protection from muscle injury, without having adequate and reliable scientific substantiation for such claims;

(i) Engaging in any of the fraudulent, unlawful, unfair, misleading and/or deceptive omissions or conduct described herein; and,

(j) Engaging in any other omissions or conduct found by the Court to be fraudulent, unlawful, unfair, misleading and/or deceptive;

7. For pre-judgment interest from the date of filing this suit;

8. For costs of the proceedings herein;

9. For reasonable attorneys' fees; and

10. Any and all such other and further relief that the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rule of Civil Procedure 38, Plaintiff, individually and on behalf of all others similarly situated, hereby demands a jury trial of any claims, causes of action or issues in this action so triable.

DATED: July 20, 2012

By: /s/ Baxter W. Banowsky

Baxter W. Banowsky
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Attornevs for Plaintiffs

EXHIBIT 1

Drugs.com

Carbaglu

Generic Name: carglumic acid
Dosage Form: tablet
FULL PRESCRIBING INFORMATION

Indications and Usage for Carbaglu

1.1 Acute hyperammonemia in patients with NAGS deficiency
Carbaglu® is indicated as an adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During acute hyperammonemic episodes concomitant administration of Carbaglu with other ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction are recommended.

1.2 Maintenance therapy for chronic hyperammonemia in patients with NAGS deficiency
Carbaglu® is indicated for maintenance therapy in pediatric and adult patients for chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be reduced or discontinued based on plasma ammonia levels.

Carbaglu Dosage and Administration

Carbaglu treatment should be initiated by a physician experienced in metabolic disorders.

2.1 Adult Dosage and Administration

The recommended initial dose for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. Concomitant administration of other ammonia lowering therapies is recommended. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms.

The recommended maintenance dose should be titrated to target normal plasma ammonia level for age. Based on limited data in 22 patients receiving maintenance treatment with Carbaglu in a retrospective case series, maintenance doses were usually less than 100 mg/kg/day.

The total daily dose should be divided into 2 to 4 doses and rounded to the nearest 100 mg. (i.e. half a Carbaglu Tablet)

2.2 Preparation for Oral Administration in Adults

Carbaglu tablets should not be swallowed whole or crushed. Disperse Carbaglu tablets in water immediately before use.

Each 200 mg tablet should be dispersed in a minimum of 2.5 ml of water and taken immediately. Carbaglu tablets do not dissolve completely in water and undissolved particles of the tablet may remain in the mixing container.

To ensure complete delivery of the dose, the mixing container should be rinsed with additional volumes of water and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

2.3 Preparation for Nasogastric Tube Administration in Adults

For patients who have a nasogastric tube in place, Carbaglu should be administered as follows:

- Mix each 200 mg tablet in a minimum of 2.5 ml of water. Shake gently to allow for quick dispersal.
- Administer the dispersion immediately through the nasogastric tube.
- Flush with additional water to clear the nasogastric tube.

2.4 Pediatric Dosage and Administration

The recommended initial dose for acute hyperammonemia is 100 mg/kg/day to 250 mg/kg/day. Concomitant administration of other ammonia lowering therapies is recommended. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms.

The recommended maintenance dose should be titrated to target normal plasma ammonia level for age. Based on limited data in 22 patients receiving maintenance treatment with Carbaglu in a retrospective case series, maintenance doses were usually less than 100 mg/kg/day.

The total daily dose should be divided into 2 to 4 doses.

2.5 Preparation for Oral Administration Using an Oral Syringe in Pediatrics

For administration via oral syringe, Carbaglu should be administered as follows:

- Mix each 200 mg tablet in 2.5 ml of water to yield a concentration of 80 mg/mL in a mixing container. Shake gently to allow for quick dispersal.
- Draw up the appropriate volume of dispersion in an oral syringe and administer immediately. Discard the unused portion.
- Refill the oral syringe with a minimum volume of water (1-2 mL) and administer immediately.

2.6 Preparation for Nasogastric Tube Administration in Pediatrics

For patients who have a nasogastric tube in place, Carbaglu should be administered as follows:

- Mix each 200 mg tablet in 2.5 ml of water to yield a concentration of 80 mg/mL in a mixing container. Shake gently to allow for quick dispersal.
- Draw up the appropriate volume of dispersion and administer immediately through a nasogastric tube. Discard the unused portion.
- Flush with additional water to clear the nasogastric tube.

Dosage Forms and Strengths

Carbaglu is a white and elongated 200 mg tablet, scored and coded "C" on one side.

Contraindications

None

Warnings and Precautions

5.1 Hyperammonemia

Any episode of acute symptomatic hyperammonemia should be treated as a life-threatening emergency. Treatment of hyperammonemia may require dialysis, preferably hemodialysis, to remove a large burden of ammonia. Uncontrolled hyperammonemia can rapidly result in brain injury/damage or death, and prompt use of all therapies necessary to reduce plasma ammonia levels is essential.

Management of hyperammonemia due to NAGS deficiency should be done in coordination with medical personnel experienced in metabolic disorders. Ongoing monitoring of plasma ammonia levels, neurological status, laboratory tests and clinical responses in patients receiving Carbaglu is crucial to assess patient response to treatment.

5.2 Therapeutic Monitoring

Plasma ammonia levels should be maintained within normal range for age via individual dose adjustment.

5.3 Nutritional Management

During acute hyperammonemic episodes, protein restriction and hypercaloric intake is recommended to block ammonia generating catabolic pathways. When plasma ammonia levels have normalized, protein intake can usually be increased with the goal of unrestricted protein intake.

Adverse Reactions

6.1 Retrospective Case Series Experience

The most common adverse reactions (occurring in ≥ 13% of patients), regardless of causality, are: vomiting, abdominal pain, pyrexia, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.
Table 1 summarizes adverse reactions occurring in 2 or more patients treated with Carbaglu in the retrospective case series. Because these reactions were reported retrospectively, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 1: Adverse Reactions Reported in > 2 Patients in the Retrospective Case Series treated with Carbaglu

System Organ Class Preferred Term	Number of Patients (N)(%)
TOTAL	23 (100)
Blood and lymphatic system disorders	
Anemia	3 (13)
Ear and labyrinth disorders	
Ear infection	3 (13)
Gastrointestinal disorders	
Abdominal pain	4 (17)
Diarrhea	3 (13)
Vomiting	6 (26)
Dysgeusia	2 (9)
General disorders and administration site conditions	
Asthenia	2 (9)
Hyperhidrosis	2 (9)
Pyrexia	4 (17)
Infections and infestations	
Infection	3 (13)
Influenza	2 (9)
Nasopharyngitis	3 (13)
Pneumonia	2 (9)
Tonsillitis	4 (17)
Investigations	
Hemoglobin decreased	3 (13)
Weight decreased	2 (9)
Metabolism and nutrition disorders	
Anorexia	2 (9)
Nervous system disorders	
Headache	3 (13)
Somnolence	2 (9)
Skin and subcutaneous tissue disorders	
Rash	2 (9)

Drug Interactions

No drug interaction studies have been performed.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well controlled studies or available human data with Carbaglu® in pregnant women. Decreased survival and growth occurred in offspring born to animals that received carglumic acid at doses similar to the maximum recommended starting human dose during pregnancy and lactation. Because untreated N-acetylglutamate synthase (NAGS) deficiency results in irreversible neurologic damage and death, women with NAGS must remain on treatment throughout pregnancy. In embryo-fetal developmental toxicity studies, pregnant rats and rabbits received oral carglumic acid during organogenesis at doses up to 1.3 times the

maximum recommended human starting dose based on body surface area (mg/m2). Actual doses were 500 and 2000 mg/kg/day (rats) and 250 and 1000 mg/kg/day (rabbits). The high doses resulted in maternal toxicity in both rats and rabbits. No effects on embryo-fetal development were observed in either species.

In a peri- and post-natal developmental study, female rats received oral carglumic acid from organogenesis through day 21 post-partum at doses up to 1.3 times the maximum recommended starting human dose based on body surface area (mg/m2). Actual doses were 500 and 2000 mg/kg/day. A reduction in offspring survival was seen at the high dose and a reduction in offspring growth was seen at both doses.

8.3 Nursing Mothers

It is not known whether Carbaglu® is excreted in human milk. Carglumic acid is excreted in rat milk, and an increase in mortality and impairment of body weight gain occurred in neonatal rats nursed by mothers receiving carglumic acid. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Carbaglu®, human milk-feeding is not recommended. Treatment is continuous and life-long for NAGS deficiency patients.

8.4 Pediatric Use

The efficacy of Carbaglu® for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who all began Carbaglu treatment during infancy or childhood. There are no apparent differences in clinical response between adults and pediatric NAGS deficiency patients treated with Carbaglu, however, data are limited.

8.5 Geriatric Use

Carbaglu has not been studied in the geriatric population. Therefore, the safety and effectiveness in geriatric patients have not been established.

Overdosage

One patient treated with 650 mg/kg/day of carglumic acid developed symptoms characterized as a monosodium glutamate intoxication-like syndrome: tachycardia, profuse sweating, increased bronchial secretion, increased body temperature and restlessness. These symptoms resolved upon reduction of dose.

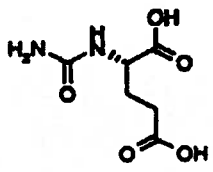
Repeated oral dosing of carglumic acid at 2000 mg/kg/day was lethal to most neonatal rats within 2-3 days of treatment. In adult rats, a single oral administration of carglumic acid was not lethal at doses up to 2800 mg/kg (1.8 times the maximum recommended starting dose based on a body surface area comparison to adult humans).

Carbaglu Description

Carbaglu tablets for oral administration contain 200 mg of carglumic acid. Carglumic acid, the active substance, is a Carbamoyl Phosphate Synthetase 1 (CPS 1) activator and is soluble in boiling water, slightly soluble in cold water, practically insoluble in organic solvents.

Chemically carglumic acid is, N-carbamoyl-L-glutamic acid or (2S)-2-(carbamoylamino) pentanedioic acid, with a molecular weight of 190.16.

The structural formula is:



Molecular Formula: C6H10N2O5

The inactive ingredients of Carbaglu are microcrystalline cellulose, sodium lauryl sulfate, hypromellose, croscarmellose sodium, silica colloidal anhydrous, sodium stearyl fumarate.

Carbaglu - Clinical Pharmacology

12.1 Mechanism of Action

Carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG), which is an essential allosteric activator of carbamoyl phosphate synthetase 1 (CPS 1) in liver mitochondria. CPS 1 is the first enzyme of the urea cycle, which converts ammonia into urea. NAG is the product of N-acetylglutamate synthase (NAGS), a mitochondrial enzyme. Carglumic acid acts as a replacement for NAG in NAGS deficiency patients by activating CPS 1.

12.2 Pharmacodynamics

In a retrospective review of the clinical course in 23 patients with NAGS deficiency, carglumic acid reduced plasma ammonia levels within 24 hours when administered with and without concomitant ammonia lowering therapies. No dose response relationship has been identified.

12.3 Pharmacokinetics

The pharmacokinetics of carglumic acid has been studied in healthy male volunteers using both radiolabeled and non-radiolabeled carglumic acid.

Absorption

The median Tmax of Carbaglu was 3 hours (range: 2-4). Absolute bioavailability has not been determined.

Distribution

The apparent volume of distribution was 2657 L (range: 1616-5797). Protein binding has not been determined.

Metabolism

A proportion of carglumic acid may be metabolized by the intestinal bacterial flora. The likely end product of carglumic acid metabolism is carbon dioxide, eliminated through the lungs.

Elimination

Median values for the terminal half-life was 5.6 hours (range 4.3-9.5), the apparent total clearance was 5.7 L/min (range 3.0-9.7), the renal clearance was 290 mL/min (range 204-445), and the 24-hour urinary excretion was 4.5 % of the dose (range 3.5-7.5). Following administration of a single radiolabeled oral dose of 100 mg/kg of body weight, 9% of the dose was excreted unchanged in the urine and up to 60% of the dose was excreted unchanged in the feces.

Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with carglumic acid.

Carglumic acid was negative in the Ames test, chromosomal aberration assay in human lymphocytes, and the in vivo micronucleus assay in rats.
There were no effects on fertility or reproductive performance in female rats at oral doses up to 2000 mg/kg/day (1.3 times the maximum recommended human starting dose based on body surface area). In a separate study, mating and fertility were unaffected in male rats at oral doses up to 1000 mg/kg/day (0.6 times the maximum recommended human starting dose based on body surface area).

Clinical Studies

14.1 Responses of Patients with NAGS Deficiency to Acute and Chronic Treatment
The efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of the clinical course of 23 NAGS deficiency patients who received Carbaglu treatment for a median of 7.9 years (range 0.6 to 20.8 years).
The demographics characteristics of the patient population are shown in Table 2.

Table 2: Baseline Characteristics of the 23 NAGS deficiency patients

		Patients N=23
Gender	Male	14 (61%)
	Female	9 (39%)
Age at initiation of Carbaglu therapy (years)	Mean (SD)	2 (4)
	Min-Max	0-13

Age groups at initiation of Carbaglu therapy	<30 days	9 (39%)
	>30 days - 11 months	9 (39%)
	≥1 - 13 years	5 (22%)
NAGS gene mutations by DNA testing	homozygous	14 (61%)
	heterozygous	4 (17%)
	Not available	5 (22%)
Patients current treatment status	On-going	18 (78%)
	Discontinued	5 (22%)

The clinical observations in the 23 patient case series were retrospective, unblinded and uncontrolled and preclude any meaningful formal statistical analyses of the data. However, short-term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days 1 to 3. Persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Table 3 summarizes the plasma ammonia levels at baseline, days 1 to 3 post-Carbaglu treatment, and long-term Carbaglu treatment for 13 evaluable patients. Of the 23 NAGS deficiency patients who received treatment with Carbaglu, a subset of 13 patients who had both well documented plasma ammonia levels prior to Carbaglu treatment and after long-term treatment with Carbaglu were selected for analysis.

All 13 patients had abnormal ammonia levels at baseline. The overall mean baseline plasma ammonia level was 271 µmol/L. By day 3, normal plasma ammonia levels were attained in patients for whom data were available. Long-term efficacy was measured using the last reported plasma ammonia level for each of the 13 patients analyzed (median length of treatment was 6 years; range 1 to 16 years). The mean and median ammonia levels were 23 µmol/L and 24 µmol/L, respectively, after a mean treatment duration of 8 years.

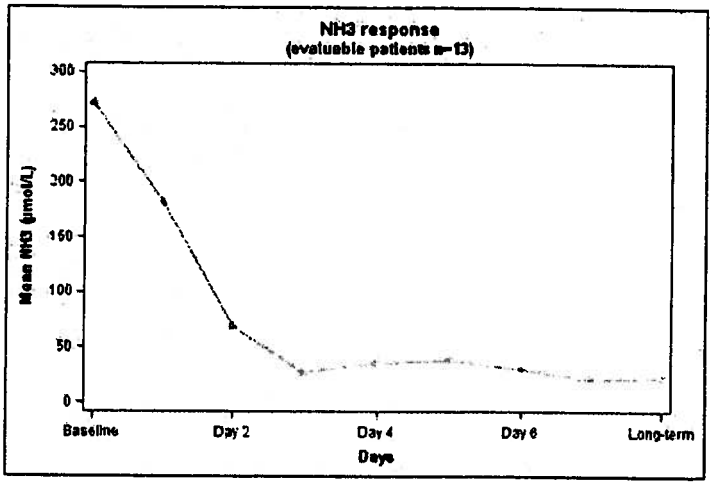
Table 3: Plasma ammonia levels at baseline and after treatment with Carbaglu

Timepoint	Statistics (N = 13*)	Ammonia** (µmol/L)
Baseline (prior to first treatment with Carbaglu)	N	13
	Mean (SD)	271 (359)
	Median	157
	Range	72-1428
	Missing Data	0
Day 1	N	10
	Mean (SD)	161 (358)
	Median	65
	Range	25-1190
	Missing Data	3
Day 2	N	8
	Mean (SD)	69 (78)
	Median	44
	Range	11-255
	Missing Data	5
Day 3	N	5
	Mean (SD)	27 (11)
	Median	25
	Range	12-42
	Missing Data	8
Long-term Mean: 8 years Median: 8 years 1 to 16 years (last available value on Carbaglu treatment)	N	13
	Mean (SD)	23 (7)
	Median	24
	Range	9-34
	Missing Data	0

*13/23 patients with complete short-term and long-term plasma ammonia documentation
**Mean ammonia normal range: 5 to 50 µmol/L

The mean plasma ammonia level at baseline and the decline that is observed after treatment with Carbaglu in 13 evaluable patients with NAGS deficiency is illustrated in Figure 1.

Figure 1: Ammonia response for 13 evaluable NAGS deficiency patients at baseline and after treatment with Carbaglu



How Supplied/Storage and Handling

How Supplied

Carbaglu is a white and elongated tablet, scored and coded "C" on one side.
Each tablet contains 200 mg of carglumic acid. Carbaglu is available in 5 or 60 tablets in a polypropylene bottle with polyethylene cap and desiccant unit.

NDC 52276-312-05 Bottle of 5 tablets
NDC 52276-312-60 Bottle of 60 tablets

Storage

Before opening, store refrigerated at 2o -8 oC (36o to 46oF).
After first opening of the container:

- Do not refrigerate, do not store above 30°C (86° F).
- Keep the container tightly closed in order to protect from moisture.
- Write the date of opening on the tablet container.
- Do not use after the expiration date stated on the tablet container.
- Discard one month after first opening.

Patient Counseling Information

Physicians should inform patients and caregivers about the following instructions for safe use of Carbaglu:

- Carbaglu tablets should not be swallowed whole or crushed. Each tablet should be dispersed in a minimum of 2.5 mL of water. Carbaglu tablets do not dissolve completely in water and undissolved particles of the tablet may remain in the mixing container. The mixing container should be rinsed with additional volumes of water and the contents swallowed immediately.
- Before opening, store in a refrigerator 2o -8 oC (36o to 46oF).
- Keep the container tightly closed in order to protect from moisture.
- After first opening of the container: do not refrigerate, do not store above 30°C (86°F).
- Write the date of opening on the tablet container. Discard one month after first opening.
- Do not use after the expiration date stated on the tablet container.

Physicians should also advise patients and caregivers that:

- When plasma ammonia levels have normalized, dietary protein intake can usually be increased with the goal of unrestricted protein intake.
- Human milk-feeding is not recommended.

- The most common adverse reactions are vomiting, abdominal pain, pyrexia, tonsilitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache.

Manufactured By: Orphan Europe SARL, Paris, France

Distributed by:

Accredo Health Group, Inc.

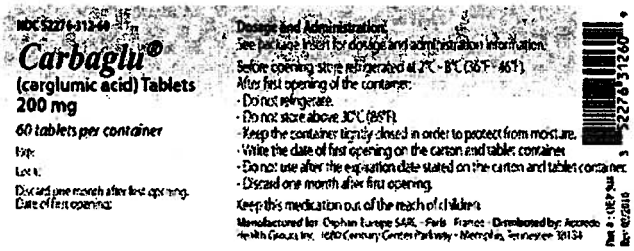
1680 Century Center Parkway

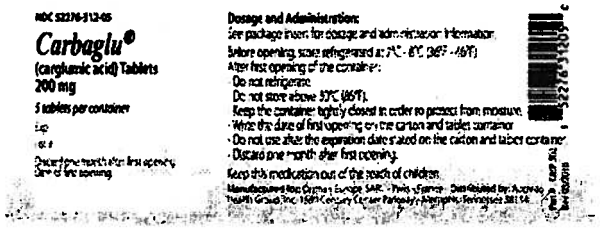
Memphis, Tennessee 38134

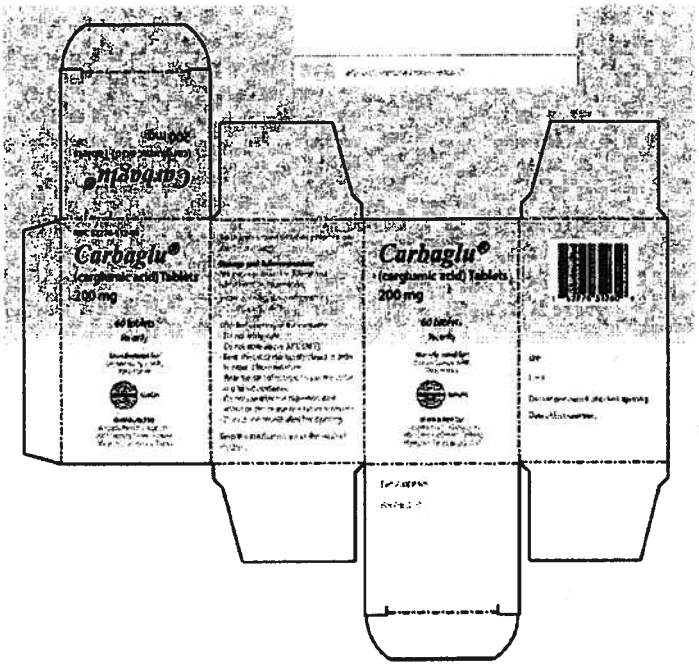
For Drug or ordering information please call Accredo Health Group Inc., Customer Service at 1-888-454-8860

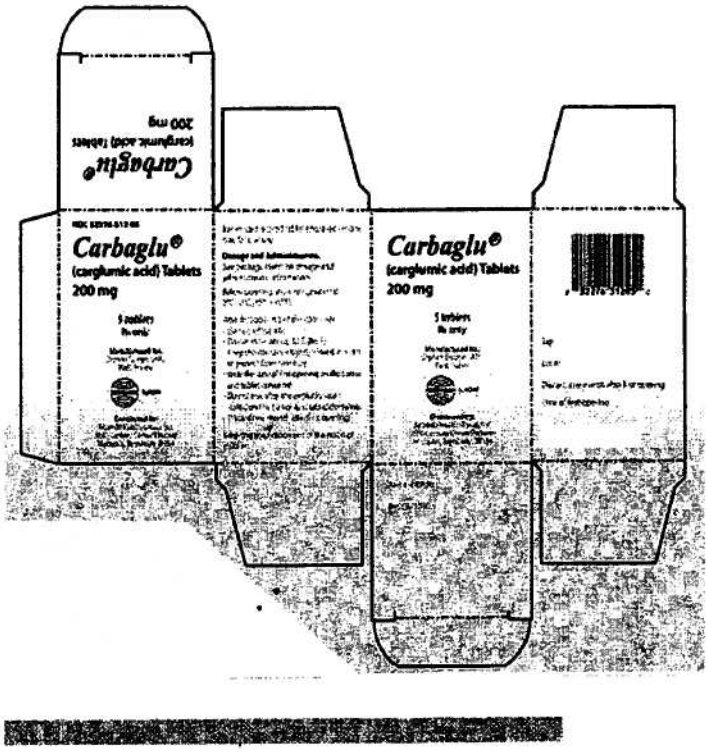
PACKAGING AND LABELING

Carbaglu Container label - 60 Tablets in Bottle






Carbaglu®
(carglumic acid) Tablets
200 mg
Carbaglu®
(carglumic acid) Tablets
200 mg


Carbaglu®
(carglumic acid) Tablets
200 mg
Carbaglu®
(carglumic acid) Tablets
200 mg

[redacted]

Product Type	HUMAN PRESCRIPTION DRUG	NDC Product Code (Source)	82276-312
Route of Administration	ORAL	DEA Schedule	

Carglumic acid (Carglumic acid)	Carglumic acid	200 mg

Cellulose, Microcrystalline	270 mg
Sodium Lauryl Sulfate	0.50 mg
Hypromellose	4.0 mg
Croscarmellose sodium	10.0 mg
Silicon Dioxide	1.5 mg
Sodium Stearyl Fumarate	5.0 mg

Color	white (Bar-shaped)	Score	3 pieces
Shape	RECTANGLE (Bar-shaped)	Size	19mm
Flavor		Imprint Code	
Contains			

#	NDC	Package Description	Multilevel Packaging
1	82276-312-05	5 TABLET in 1 BOTTLE	None
2	82276-312-60	60 TABLET in 1 BOTTLE	None

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022562	03/18/2010	

Labeler - Orphan Europe, SARL (767598352)

Registrant - Orphan Europe, SARL (767598352)

Establishment

Name	Address	ID/FEI	Operations
Orphan Europe, SARL		767598352	manufacture

Revised: 11/2010 Orphan Europe, SARL

More Carbaglu resources

- Carbaglu Side Effects (in more detail)
- Carbaglu Dosage
- Carbaglu Support Group
- 0 Reviews for Carbaglu - Add your own review/rating

Carbaglu Consumer Overview
Carbaglu MedFacts Consumer Leaflet (Wolters Kluwer)
Carglumic Acid Professional Patient Advice (Wolters Kluwer)
carglumic acid Advanced Consumer (Micromedex) - Includes Dosage Information

Compare Carbaglu with other medications

Hyperammonemia

EXHIBIT 2

Tainted Products Marketed as Dietary Supplements

On Dec. 15, 2010, the Food and Drug Administration (FDA) took new steps aimed at keeping consumers safe from harmful products that are marketed as dietary supplements and that contain undeclared or deceptively labeled ingredients.

FDA has found that these products are often promoted for weight loss, sexual enhancement, and bodybuilding.

The new steps FDA has taken include:

- A letter from Commissioner of Food and Drugs Margaret A. Hamburg to the dietary supplement industry emphasizing its legal obligation and responsibilities to prevent tainted products from reaching the U.S. market.
- A new rapid public notification (*www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/TDS/rss.xml*) system on its website to more quickly warn consumers about these products.
- A mechanism for industry to alert FDA about potentially tainted products and about the firms that make them.

A History of Action

Among the substances found in products that are marketed as dietary supplements and that contain hidden or deceptively labeled ingredients are

- the active ingredients in FDA-approved drugs or their analogs (closely-related drugs).
- other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients.

Where FDA investigations have discovered tainted products marketed as dietary supplements, the agency has issued warning letters and conducted seizures and criminal prosecutions.

FDA has also alerted consumers to hundreds of products with these often deceptively labeled and harmful ingredients, including more than 80 products marketed for sexual enhancement, more than 70 products marketed for weight loss, and more than 80 products marketed for bodybuilding.

Advice for Consumers

Michael Levy, director of FDA's Division of New Drugs and Labeling Compliance, says labeling of these tainted products may claim that they are "alternatives" to FDA-approved drugs, or "legal" alternatives to anabolic steroids.

"Consumers should avoid products marketed as supplements that claim to have effects similar to prescription drugs," Levy says. "Consumers should also be wary of products with labeling only in a foreign language or that are marketed through mass e-mails."

In all, consumers should heed these potential warning signs of tainted products marketed as dietary supplements.

- Products claiming to be alternatives to FDA-approved drugs or to have effects similar to prescription drugs.
- Products claiming to be a legal alternative to anabolic steroids.
- Products that are marketed primarily in a foreign language or those that are marketed through mass e-mails.
- Sexual enhancement products promising rapid effects such as working in minutes to hours, or long-lasting effects such as 24 hours to 72 hours.
- Products that provide warnings about testing positive in performance enhancement drug tests.

Generally, if you are using or considering using any product marketed as a dietary supplement, FDA suggests that you

- check with your health care professional or a registered dietician on any nutrients you may need in addition to your regular diet
- ask yourself: Does it sound too good to be true?
  - Be cautious if the claims for the product seem exaggerated or unrealistic
  - Watch out for extreme claims—for example, "quick and effective," "cure-all;" "can treat or cure diseases; or "totally safe"
  - Be skeptical about anecdotal information from personal "testimonials" about incredible benefits or results obtained from using a product
- ask your health care professional for help distinguishing between reliable and questionable information

Find this and other Consumer Updates at *www.fda.gov/ForConsumers/ConsumerUpdates*

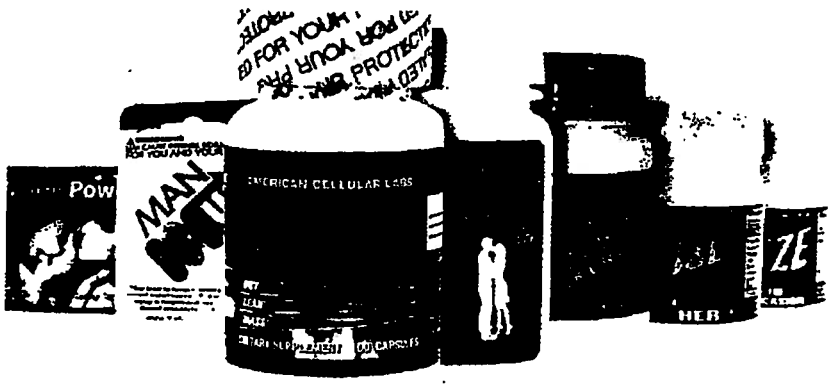
Sign up for free e-mail subscriptions at *www.fda.gov/consumer/consumerenews.html*

EXHIBIT 3

Consumer Health Information
www.fda.gov/consumer

Beware of Fraudulent 'Dietary Supplements'

Federal regulators continue to warn consumers about tainted, dangerous products that are marketed as dietary supplements. These fraudulent products can cause serious injury or even death.



The Food and Drug Administration (FDA) has found nearly 300 fraudulent products—promoted mainly for weight loss, sexual enhancement, and bodybuilding—that contain hidden or deceptively labeled ingredients, such as

- the active ingredients in FDA-approved drugs or their analogs (closely-related drugs)
- other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients

"These products are masquerading as dietary supplements—they may look like dietary supplements but they are not legal dietary supplements," says Michael Levy, director of FDA's Division of New Drugs and Labeling Compliance. "Some of these products contain hidden prescription ingredients at levels much higher than those found in an approved drug product and are dangerous."

FDA has received numerous reports of harm associated with the use of these products, including stroke, liver injury, kidney failure, heart palpitations, and death.

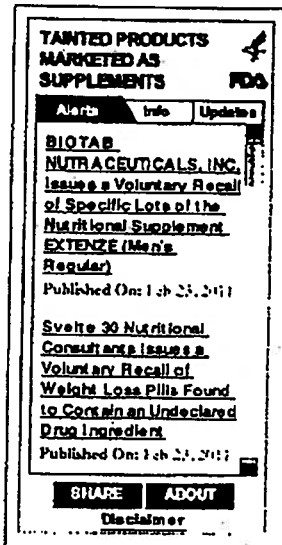
Advice for Consumers

"We need consumers to be aware of these dangerous products and to learn how to identify and avoid them," says Levy. Consumers should look for potential warning signs of tainted products marketed as dietary supplements, such as

- products claiming to be alternatives to FDA-approved drugs or to have effects similar to prescription drugs
- products claiming to be a legal alternative to anabolic steroids
- products that are marketed primarily in a foreign language or those that are marketed through mass e-mails
- sexual enhancement products promising rapid effects, such as working in minutes to hours, or long-lasting effects, such as working for 24 to 72 hours
- product labels warning that you may test positive in performance enhancement drug tests

Generally, if you are using or considering using any product marketed as a dietary supplement, FDA suggests that you

- check with your health care professional or a registered dietician about any nutrients you may need in addition to your regular diet
- ask your health care professional for help distinguishing between reliable and questionable information
- ask yourself if it sounds too good to be true
  - Be cautious if the claims for the product seem exaggerated or unrealistic.
  - Watch out for extreme claims—for example, "quick and effective," "cure-all," "can treat or cure diseases," or "totally safe."
  - Be skeptical about anecdotal information from personal "testimonials" about incredible benefits or results obtained from using a product.



Keep Up-to-Date on Tainted Products

Get the latest news on tainted products by using FDA's "widget" (*www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/ucm242603.htm*) and "RSS feed" (*www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/TDS/tds.xml*). Both of these online tools contain alerts, health information, and FDA actions on tainted products marketed as dietary supplements.

A widget is a portable application that displays featured content directly on a web page. Bloggers or owners of websites can embed this content into their sites. Once FDA's widget is added, there's no technical maintenance—FDA will automatically provide updates to content displayed on the widget.

The RSS (Really Simple Syndication) feed, like the widget, includes updated content published on FDA's website. RSS is usually used for news and blog websites and requires an RSS news reader (a special software program) to pick up the content in the feed. Organizations and bloggers can subscribe to the RSS feed to receive updates automatically and put together their own customized lists of news and information.

- See FDA's website (*www.fda.gov/weightlossfraud*) to help recognize fraudulent weight-loss products and claims.

If you suspect a dietary supplement sold online may be illegal, FDA urges you to report that information online (*www.fda.gov/Safety/ReportaProblem/ucm059315.htm*). In addition, you or your health care professional can also report an illness or injury you believe to be related to the use of a dietary supplement by phone at 1-800-FDA-1088 or online (*www.fda.gov/Safety/ReportaProblem/ucm053074.htm*).

Dietary Supplements and FDA

Dietary supplements, in general, are not FDA-approved. Under the law (Dietary Supplement Health and Education Act of 1994), dietary supplement firms do not need FDA approval prior to marketing their products. It is the company's responsibility to make sure its products are safe and that any claims are true.

Just because you see a supplement product on a store shelf does NOT mean it is safe or effective. When safety issues are suspected, FDA must investigate and, when warranted, take steps to have the product removed from the market. However, it is much easier for a firm to get a product on the market than it is for FDA to take a product off the market.

FDA has worked with industry to recall numerous products with potentially harmful ingredients including

- more than 40 products marketed for weight loss
- more than 70 products marketed for sexual enhancement
- more than 80 products marketed for body building

FDA last alerted the public to tainted products in December 2010, and will continue to issue consumer alerts and press announcements about these products. The agency has issued warning letters, seized products, and conducted criminal prosecutions. In December 2010, a woman pleaded guilty to an 18-count indictment charging her with the illegal importation and distribution of more than four million diet pills that contained a controlled substance, unapproved drugs, and a possible cancer-causing agent.

Remember, FDA cannot test all products on the market to identify those that contain potentially harmful hidden ingredients. Consumers must also be aware of these dangerous products and learn how to identify and avoid them using the warning signs described above. FDA

Find this and other Consumer Updates at *www.fda.gov/ForConsumers/ConsumerUpdates*

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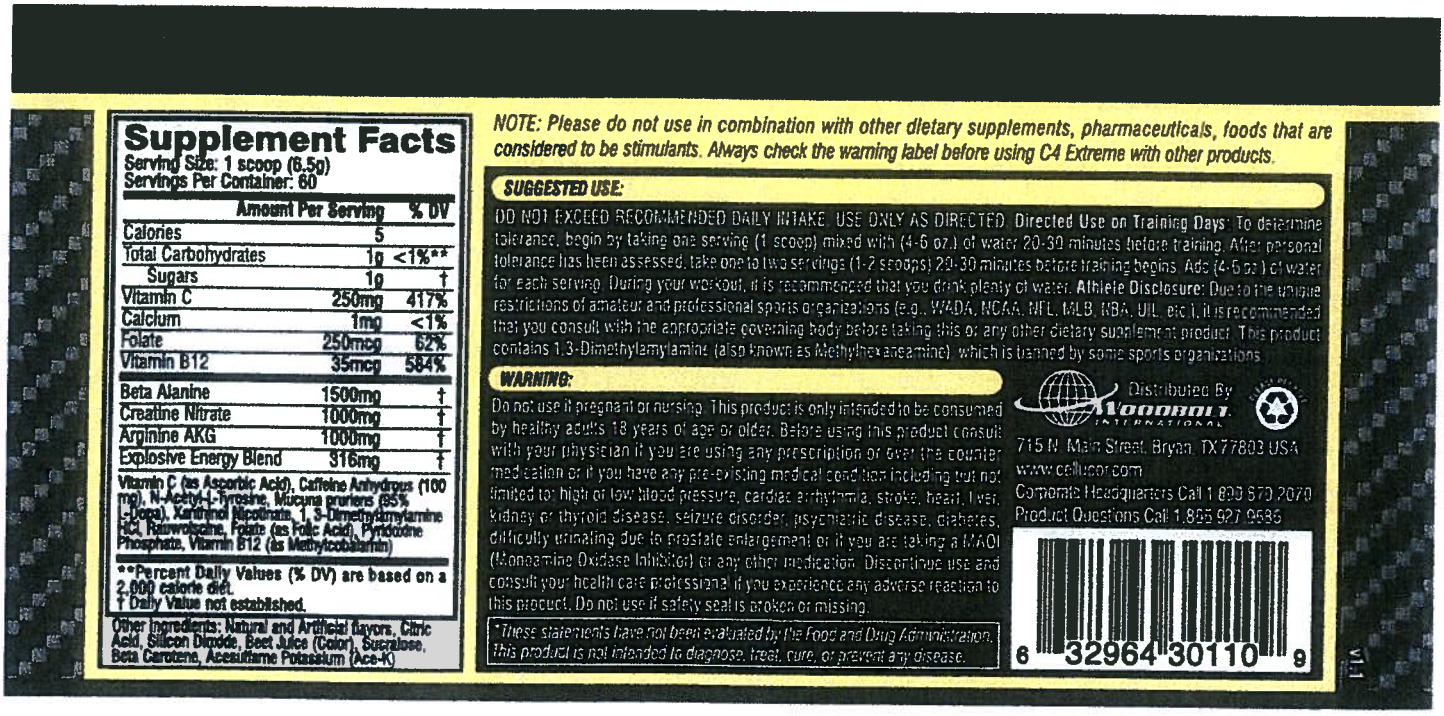
EXHIBIT 4


CELLUCOR
C4
EXTREME
FRUIT PUNCH
PRE-WORKOUT
w/NO3
EXPLOSIVE
WORKOUTS
CONTAINS CREATINE NITRATE
60 SERVINGS
DIETARY SUPPLEMENT | Net. Wt. 390g
Supplement Facts
NOTE: Please do not use in combination with other dietary supplements, pharmaceuticals, foods that are considered to be stimulants. Always check the warning label before using C4 Extreme with other products.
WARNING:



Supplement Facts

Serving Size: 1 scoop (6.5g)
Servings Per Container: 60

Amount Per Serving		% DV
Calories	5	
Total Carbohydrates	1g	<1%**
Sugars	1g	†
Vitamin C	250mg	417%
Calcium	1mg	<1%
Folate	250mcg	62%
Vitamin B12	35mcg	584%
Beta Alanine	1500mg	†
Creatine Nitrate	1000mg	†
Arginine AKG	1000mg	†
Explosive Energy Blend	916mg	†

Vitamin C (as Ascorbic Acid), Caffeine Anhydrous (100 mg), N-Acetyl-L-Tyrosine, Mucuna pruriens (95% L-Dopa), Xanthinol Nicotinate, 1,3-Dimethylamylamine HCl, Rauwolscine, Folate (as Folic Acid), Pyridoxine Phosphate, Vitamin B12 (as Methylcobalamin)

**Percent Daily Values (% DV) are based on a 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Natural and Artificial Flavors, Citric Acid, Silicon Dioxide, Beet Juice (Color), Sucralose, Beta Carotene, Acesulfame Potassium (Ace-K)

NOTE: Please do not use in combination with other dietary supplements, pharmaceuticals, foods that are considered to be stimulants. Always check the warning label before using C4 Extreme with other products.

SUGGESTED USE:

DO NOT EXCEED RECOMMENDED DAILY INTAKE. USE ONLY AS DIRECTED. Directed Use on Training Days: To determine tolerance, begin by taking one serving (1 scoop) mixed with (4-6 oz.) of water 20-30 minutes before training. After personal tolerance has been assessed, take one to two servings (1-2 scoops) 20-30 minutes before training begins. Add (4-6 oz.) of water for each serving. During your workout, it is recommended that you drink plenty of water. **Athlete Disclosure:** Due to the unique restrictions of amateur and professional sports organizations (e.g., WADA, NCAA, NFL, MLB, NBA, UIL, etc.), it is recommended that you consult with the appropriate governing body before taking this or any other dietary supplement product. This product contains 1,3-Dimethylamylamine (also known as Methylhexaneamine) which is banned by some sports organizations.

WARNING:

Do not use if pregnant or nursing. This product is only intended to be consumed by healthy adults 18 years of age or older. Before using this product consult with your physician if you are using any prescription or over the counter medication or if you have any pre-existing medical condition including but not limited to: high or low blood pressure, cardiac arrhythmia, stroke, heart, liver, kidney or thyroid disease, seizure disorder, psychiatric disease, diabetes, difficulty urinating due to prostate enlargement or if you are taking a MAOI (Monoamine Oxidase Inhibitor) or any other medication. Discontinue use and consult your health care professional if you experience any adverse reaction to this product. Do not use if safety seal is broken or missing.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Distributed By
Cellucor International

715 N. Main Street, Bryan, TX 77803 USA
www.cellucor.com
Corporate Headquarters Call 1 800 570 2070
Product Questions Call 1.866.927.9636

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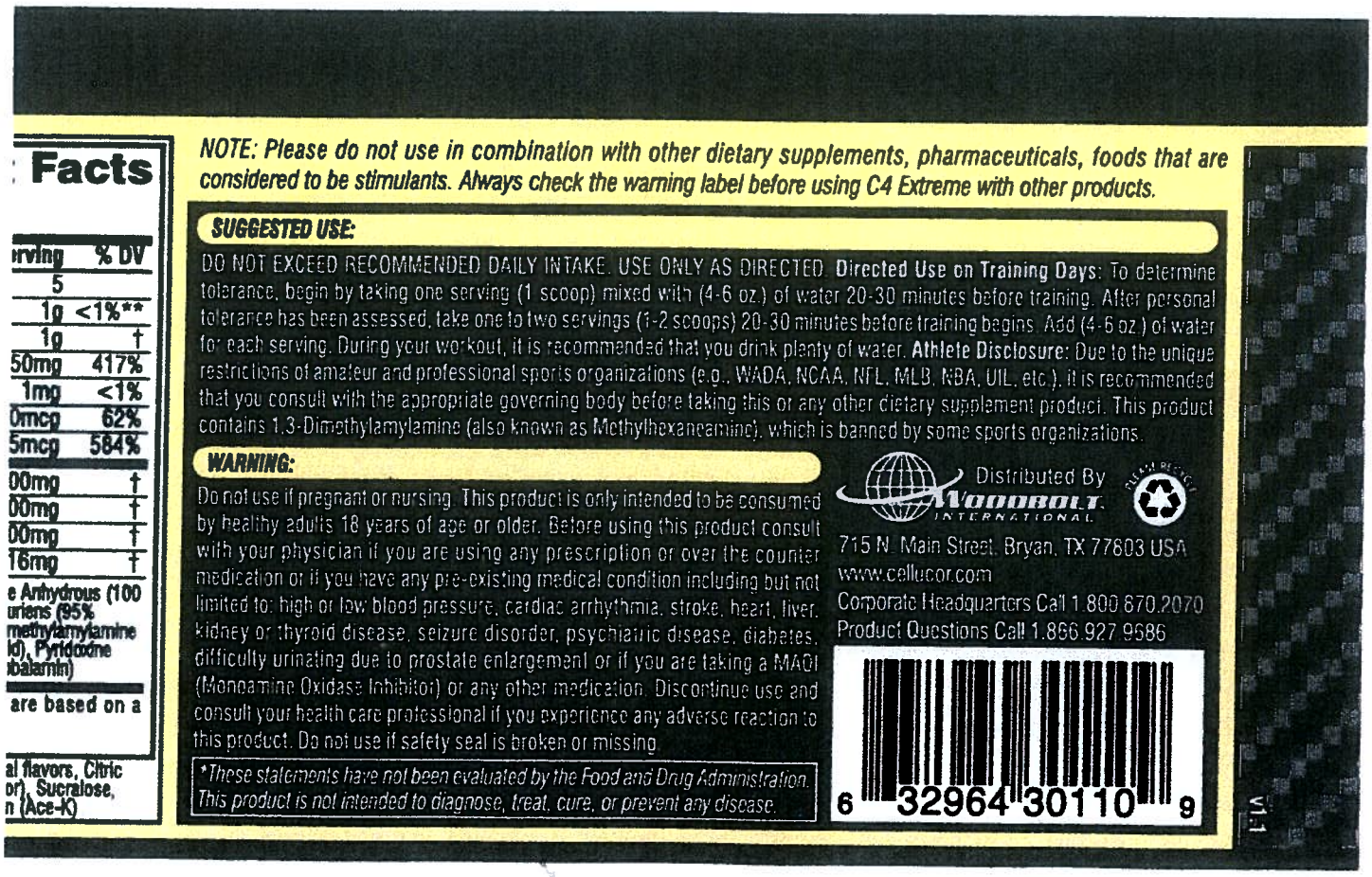

Facts

rving	% DV
5	
1g	<1%**
1g	†
50mg	417%
1mg	<1%
0mcg	62%
5mcg	584%
00mg	†
00mg	†
00mg	†
16mg	†

e Anhydrous (100 urients (95% methylamylamine id), Pyridoxine obalamin)

are based on a

al flavors, Citric or), Sucralose, n (Ace-K)

NOTE: Please do not use in combination with other dietary supplements, pharmaceuticals, foods that are considered to be stimulants. Always check the warning label before using C4 Extreme with other products.

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**These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.*

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Woodbolt International

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www.cellucor.com
Corporate Headquarters Call 1.800.870.2070
Product Questions Call 1.866.927.9686

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V11

EXHIBIT 5


CELLUCOR
M5
EXTREME
FRUIT PUNCH
IGNITE + BUILD
2 PRODUCTS IN 1
2 IN 1 CUSTOM PRE-WORKOUT W/NO3
THE MASS MACHINE
EXPLOSIVE ENERGY IGNITED BY C4
MUSCLE PUMPS*
STRENGTH & SIZE*
MUSCLE MASS*
30 CUSTOMIZABLE WORKOUTS
DIETARY SUPPLEMENT | Net Wt. 7.76y (1.58 lbs)
CUSTOMIZE YOUR WORKOUT:
FOR EXPLOSIVE ENERGY OR MAXIMUM MUSCLE PUMPS
(2) SCOOPS IGNITE + (1) SCOOP BUILD
FOR EXPLOSIVE ENERGY, MAXIMUM MUSCLE PUMPS AND STRENGTH
(1) SCOOP IGNITE + (1) SCOOP BUILD
FOR EXPLOSIVE ENERGY OR MAXIMUM MUSCLE PUMPS AND STRENGTH
(1) SCOOP IGNITE + (1) SCOOP BUILD
PEEL HERE
2 PRODUCTS IN 1
IGNITE + BUILD
IGNITE
Supplement Facts
BUILD
Supplement Facts


CUSTOMIZE YOUR WORKOUT:
FOR EXPLOSIVE ENERGY AND GROWTH
2 SCOOPS IGNITE
+
1 SCOOP BUILD
FOR FOCUSED ENERGY OR NIGHT TIME WORKOUTS
1 SCOOP IGNITE
+
1 SCOOP BUILD
2 PRODUCTS IN 1
IGNITE
+
BUILD
PEEL HERE
IGNITE
Supplement Facts
Serving Size: 1 scoop (Oz) Servings Per Container: 60
Amount Per Serving % DV
Folate 250mcg 62%
Vitamin B12 35mcg 584%
Beta Alanine 1500mg †
Explosive Energy Blend 2666mg †
Caffeine Anhydrous (100 mg), N-Acetyl-L-Tyrosine, Mucuna pruriens (95% L-Dopa), Xanthinol Nicotinate, 1,3-Dimethylamylamine HCl, Rauwolscine, Folate (as Folic Acid), Pyridoxine Phosphate, Vitamin B12 (as Methylcobalamin)
† Daily Value not established.
Other Ingredients: Citric Acid, Sucralose, Artificial Flavor, Silicon Dioxide
BUILD
Supplement Facts
Serving Size: 1 scoop (19.75g) Servings Per Container: 30
Amount Per Serving % DV
Calories 35
Total Carbohydrates 1g <1%**
Protein 1g 2%**
Vitamin C 500mg 833%
Magnesium 200mg 50%
L-Leucine 5000mg †
Arginine AKG 3000mg †
Creatine Nitrate 2500mg †
Creatine MagnaPower® Magnesium Creatine Chelate 2500mg †
Betaine HCl 1000mg †
L-Citrulline 1000mg †
Ornithine AKG 500mg †
Grape Seed extract 200mg †
Bis-(picolinato) Oxovanadium 15mg †
**Percent Daily Values (% DV) are based on a 2,000 calorie diet.
† Daily Value not established.
Other Ingredients: Natural and Artificial Flavors, Citric Acid, Malic Acid, Silicon Dioxide, Sucralose, Beet Juice (Color), Acesulfame Potassium (Ace-K)
Creatine MagnaPower® is a registered trademark of Albion Laboratories, Inc. and is covered by U.S. Patent 6,114,379 and patents pending.
NOTE: Please do not use in combination with other dietary supplements, pharmaceuticals, foods that are considered to be stimulants. Always check the warning label before using MS EXTREME with other products. Do not exceed recommended daily intake. Use only as directed.
SUGGESTED USE:
WARNING:
*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
715 N. Main Street
Bryan, TX 77803 USA
Corporate Headquarters:
Product Questions:
6 32964 30201 4


CUSTOMIZE YOUR WORKOUT:
FOR EXPLOSIVE ENERGY AND GROWTH
2 SCOOPS IGNITE
+
1 SCOOP BUILD
FOR FOCUSED ENERGY OR NIGHT TIME WORKOUTS
1 SCOOP IGNITE
+
1 SCOOP BUILD
2 PRODUCTS IN 1
IGNITE
+
BUILD
PEEL HERE
IGNITE
Supplement Facts
Serving Size: 1 scoop (2g) Servings Per Container: 60
Amount Per Serving % DV
Folate 250mcg 62%
Vitamin B12 35mcg 584%
Beta Alanine 1500mg †
Explosive Energy Blend 266mg †
Caffeine Anhydrous (100 mg), N-Acetyl-L-tyrosine, Mucuna pruriens (95% L-Dopa), Xanthinol Nicotinate, 1,3-Dimethylamylamine HCl, Rauwolscine, Folate (as Folic Acid), Pyridoxine Phosphate, Vitamin B12 (as Methylcobalamin)
† Daily Value not established.
Other Ingredients: Citric Acid, Sucralose, Artificial Flavor, Silicon Dioxide
BUILD
Supplement Facts
Serving Size: 1 scoop (19.75g) Servings Per Container: 30
Amount Per Serving % DV
Calories 35
Total Carbohydrates 1g <1%**
Protein 1g 2%**
Vitamin C 500mg 833%
Magnesium 200mg 50%
L-Leucine 5000mg †
Arginine AKG 3000mg †
Creatine Nitrate 2500mg †
Creatine MagnaPower® Magnesium Creatine Chelate 2500mg †
Betaine HCl 1000mg †
L-Citrulline 1000mg †
Ornithine AKG 500mg †
Grape Seed extract 200mg †
Bis(picolinato) Oxovanadium 15mg †
**Percent Daily Values (% DV) are based on a 2,000 calorie diet.
† Daily Value not established.
Other Ingredients: Natural and Artificial Flavors, Citric Acid, Malic Acid, Silicon Dioxide, Sucralose, Beet Juice (Color), Acesulfame Potassium (Ace-K)
Creatine MagnaPower® is a registered trademark of Albion Laboratories, Inc, and is coveredby U.S. Patent 6,114,379 and patents pending.
NOTE: Please do not use in combination with other dietary supplements, pharmaceuticals, foods that are considered to be stimulants. Always check the warning label before using M5 EXTREME with other products. Do not exceed recommended daily intake. Use only as directed.
SUGGESTED USE:
M5's 2 in 1 container allows you to customize your workout. Always take 1 (Blue) scoop of the "Build" compartment (located on bottom) with 1-2 (yellow) scoops of the "Ignite" compartment (located on top) 30 minutes prior to training. Mix with 10-12 ounces of water depending on taste preference. Athlete Disclosure: Due to the unique restrictions of amateur and professional sports organizations (e.g. WADA, NCAA, NFL, MLB, NBA, UFL, etc.), it is recommended that you consult with the appropriate governing body before taking this or any other dietary supplement product. This product contains 1,3-Dimethylamylamine (also known as Methylhexaneamine), which is banned by some sports organizations.
WARNING:
Do not use if pregnant or nursing. This product is only intended to be consumed by healthy adults 18 years of age or older. Before using this product consult with your physician if you are using any prescription or over the counter medication or if you have any pre-existing medical condition including but not limited to: high or low blood pressure, cardiac arthythmia, stroke, heart, liver, kidney or thyroid disease, seizure disorder, psychiatric disease, diabetes, difficulty urinating due to prostate enlargement or if you are taking a MAOI (Monoamine Oxidase Inhibitor) or any other medication. Discontinue use and consult your health care professional if you experience any adverse reaction to this product. Do not use if safety seal is broken or missing.
*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
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Product Questions:
6 32964 30201 4

EXHIBIT 6


CELLUCOR
NO
N-ZERO
EXTREME
FRUIT PUNCH
CREATINE FREE
PRE-WORKOUT
THE
LEAN
MACHINE
EXPLOSIVE ENERGY*
MUSCLE PUMPS*
STRENGTH & DEFINITION*
MUSCLE PROTECTION*
30 SERVINGS
DIETARY SUPPLEMENT | Net Wt. 277g (0.6 lbs)
Supplement Facts
Serving Size 1 Scoop (14.4g)
Servings Per Container 30
Amount Per Servings % DV
Distributed by
Cellucor
Dallas, TX 77063 USA
www.cellucor.com
1.800.FALSTR
1.800.FALSTR
32964 20071 8

NOTE: Please do not use in conjunction with other dietary supplements, pharmaceuticals, foods that are considered to be stimulants. Always check the warning label before using NO EXTREME with other products. Do not exceed recommended daily intake. Use only as directed.

SUGGESTED USE:

As a dietary supplement for adults, use for up to 8 weeks in a cycle, then discontinue use for 2 weeks before retaking the product. Mix one scoop with 8 fl. oz. of water. Do not take with food. STORE IN A COOL DRY PLACE. **WORK-OUT DAYS:** Take 1 serving (1 scoop) 30 minutes pre-workout. **Athlete Disclosure:** Due to the unique restrictions of amateur and professional sports organizations (WADA, NCAA, NFL, MLB, NBA, UIL, etc.) it is recommended that you consult with the appropriate governing body before taking this or any other dietary supplement.

WARNING:

DO NOT USE IF PREGNANT OR NURSING. This product is only intended to be consumed by healthy adults 18 years of age or older. Before using this product consult with your physician if you are using any prescription or over the counter medication or if you have any pre-existing medical condition including but not limited to: high or low blood pressure, cardiac arrhythmia, stroke, heart, liver, kidney or thyroid disease, seizure disorder, psychiatric disease, diabetes, difficulty urinating due to prostate enlargement or if you are taking a MAOI (Monoamine Oxidase Inhibitor) or any other medication. Discontinue use and consult your health care professional if you experience any adverse reaction to this product. Do not use if safety seal is broken or missing.

Supplement Facts

Serving Size: 1 Scoop (9.24g)
Servings Per Container: 30

	Amount Per Serving	% DV
NO Extreme Blend		†
L-Arginine AKG	2000mg	†
Beta Alanine	1500mg	†
Carbamyl-L-Glutamate	1000mg	†
L-Citrulline Malate	500mg	†
L-Ornithine AKG	500mg	†
L-Norvaline	100mg	†
Thermal Energy Blend	1511mg	†
L-Leucine, L-Histidine HCl, L-Isoleucine, L-Valine, Caffeine (150 mg of Caffeine Anhydrous), Picamilon, Cinnamon Bark powder, Theobromine (50 mg), Magnesium Tanshinonate, Synephrine HCl, Methylpyramine, Oxpurandum, Vinpocetine		

† Daily Value (DV) not established.

Other Ingredients: Citric Acid, Natural and Artificial flavors, beet color, Sucralose, silica, Acesulfame Potassium.

**These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.*

Distributed By Nanobolt International

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EXHIBIT 7

U.S. Food and Drug Administration

Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues

Back to Dietary Supplements Guidance

Contains Nonbinding Recommendations
Draft-Not for Implementation

July 2011

This guidance is being distributed for comment purposes only.

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-2375.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
July 2011

Contains Nonbinding Recommendations
Draft-Not for Implementation

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Guidance for Industry[1]
Dietary Supplements: New Dietary Ingredient Notifications and Related Issues

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

This guidance is intended to assist industry in deciding when a premarket safety notification for a dietary supplement containing a new dietary ingredient (NDI) is necessary and in preparing premarket safety notifications (also referred to as "NDI notifications"). The guidance addresses in question and answer format what qualifies as a NDI, when a NDI notification is necessary, the procedures for submitting a NDI notification, the types of data and information that FDA recommends manufacturers and distributors consider when they evaluate the safety of a dietary supplement containing a NDI, and what should be included in a NDI notification. In addition, the guidance contains questions and answers about parts of the dietary supplement definition that can affect whether a particular substance may be marketed as a dietary ingredient in a dietary supplement. The agency encourages manufacturers and distributors to consult this guidance during their safety review of a dietary supplement that contains a NDI and in preparing NDI notifications.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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II. Background

On October 25, 1994, the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Pub. L. 103-417) was signed into law.DSHEA amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) by adding, among other provisions, (1) section 201(ff) (21 U.S.C. 321(ff)), which defines the term "dietary supplement"; and (2) section 413 (21 U.S.C. 350b), which defines the term "new dietary ingredient" and requires the manufacturer or distributor of a NDI, or of the dietary supplement that contains the NDI, to submit a premarket notification to FDA at least 75 days before introducing the supplement into interstate commerce or delivering it for introduction into interstate commerce, unless the NDI and any other dietary ingredients in the dietary supplement "have been present in the food supply as an article used for food in a form in which the food has not been chemically altered" (21 U.S.C. 350b (a)(1)).The notification must contain the information, including any citation to published articles, which is the basis on which the manufacturer or distributor of the NDI or dietary supplement (the notifier) has concluded that the dietary supplement containing the NDI will reasonably be expected to be safe.If the required premarket notification is not submitted to FDA, section 413(a) of the FD&C Act provides that the dietary supplement containing the NDI is deemed to be adulterated under section 402(f) of the FD&C Act (21 U.S.C. 342(f)).Even if the notification is submitted as required, the dietary supplement containing the NDI is adulterated under section 402(f) unless there is a history of use or other evidence of safety establishing that the NDI, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.

To assist industry in complying with DSHEA, FDA issued a regulation in 21 CFR 190.6 (section 190.6 or the NDI regulation) to implement the FD&C Act's premarket notification requirements for dietary supplements that contain a NDI (62 FR 49886; September 23, 1997). The NDI regulation specifies the information the manufacturer or distributor must include in its premarket NDI notification (21 CFR 190.6(b)):

- The name and complete address of the manufacturer or distributor that is submitting the notification.
- The name of the NDI that is the subject of the premarket notification. For botanicals, the Latin binomial name must be given, including the author citation (the name of the scientist who gave the botanical its Latin binomial name).
- A description of the dietary supplement that contains the NDI, including:
    - the level of the NDI in the dietary supplement, and
    - the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the supplement's labeling, the ordinary conditions of use of the supplement.
- The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended in the labeling of the dietary supplement, will reasonably be expected to be safe.
- The signature of a person authorized by the manufacturer or distributor to sign the notification on its behalf.

In addition to the requirements for the content of NDI notifications, the NDI regulation also establishes the administrative procedures for these notifications. Section 190.6(c) defines the filing date of a notification as the date the agency receives it and, consistent with section 413(a)(2) of the FD&C Act, prohibits the manufacturer or distributor of the dietary supplement that contains the NDI from introducing, or delivering for introduction, the dietary supplement into interstate commerce for 75 days after the filing date (21 CFR 190.6(c)). Section 190.6(d) provides for the assignment of a new notification filing date that resets the 75-day period when the manufacturer or distributor submits additional substantive information in support of the original NDI notification. Consistent with section 413(a) of the Act, section190.6(e) provides that FDA will not disclose the existence of, or the information contained in, a NDI notification for 90 days after the filing date of the notification. Section 190.6(e) further provides that, after the 90th day, the entire notification, except trade secrets and confidential commercial information, will be placed on public display, as prescribed in section 413(a) of the Act. Finally, section 190.6(f) states that FDA's failure to respond to a NDI notification does not constitute a finding by the agency that the NDI or the dietary supplement containing the NDI is safe or is not adulterated under section 402 of the Act (21 U.S.C. 342).

On January 4, 2011, the President signed into law the FDA Food Safety Modernization Act (FSMA) (Public Law 111-353). Section 113(b) of FSMA requires FDA to publish, not later than 180 days after the date of enactment, guidance that clarifies when a dietary supplement ingredient is a NDI, when the manufacturer or distributor of a dietary ingredient or dietary supplement should submit a NDI notification to FDA under section 413(a)(2) of the FD&C Act, the evidence needed to document the safety of a NDI, and appropriate methods for establishing the identity of a NDI. This draft guidance is being published to comply with section 113(b).

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III. Scope of the Guidance

FDA's goal in promulgating the NDI regulation was to ensure that NDI notifications contained the information that would enable FDA to evaluate whether a

dietary supplement containing a NDI is reasonably expected to be safe. After having gained some experience with the NDI notifications that have been submitted to the agency and from the many questions that industry has asked since the agency's regulation implementing the NDI notification requirement was issued, FDA has concluded that this guidance is needed to assist industry in achieving this goal.

DSHEA does not specify the type or amount of evidence that must be included in a NDI notification. The purpose of this guidance is to give manufacturers and distributors of these products information and recommendations to help them decide when a NDI notification is necessary and to improve the quality and quantity of NDI notifications. There are an estimated 55,600 dietary supplement products on the market, and FDA has received approximately 700 NDI notifications since we began reviewing NDI notifications approximately 16 years ago.[2] Additionally, the Institute of Medicine has estimated that 1,000 new dietary supplements are introduced to the market each year.[3] These figures, coupled with recent concern by both the agency and industry regarding the presence of undeclared active ingredients in products marketed as dietary supplements, highlight the necessity for marketers of dietary supplements to submit NDI notifications as an important preventive control to ensure that the consumer is not exposed to potential unnecessary public health risks in the form of new ingredients with unknown safety profiles.[4]

This guidance answers frequently asked questions about NDI notifications and related issues. It also makes recommendations to industry for preparing better NDI notifications that the agency will be able to review more efficiently, which should result in quicker response times. The agency recommends that the data and information that are submitted should include (1) a full description of the identity and composition of the NDI and the dietary supplement in which it will be marketed, (2) a discussion of the basis for the notifier's conclusion that the substance is a NDI, (3) a description of the conditions of use recommended or suggested in the labeling of the dietary supplement, or, if no conditions of use are recommended or suggested in the labeling, the ordinary conditions of use of the supplement, and (4) an explanation of how the history of use or other evidence of safety in the notification justifies the notifier's conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe.

This draft guidance focuses on interpreting the FD&C Act's requirements relating to NDIs and dietary supplements that contain a NDI. It does not discuss other parts of the FD&C Act that may affect the regulatory status of a particular ingredient or product, such as provisions of the recently enacted FSMA[5] that may apply to dietary ingredients and/or dietary supplements.

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IV. Determining Whether a New Dietary Ingredient (NDI) Notification is Necessary

A. When Is a Dietary Ingredient New?

1. **Is a dietary ingredient that was not marketed in the U.S. before October 15, 1994, a new dietary ingredient (NDI)?**

   Yes. A NDI is defined by statute as "a dietary ingredient that was not marketed in the United States before October 15, 1994."[6]

2. **Do I need to submit a NDI notification for a dietary ingredient marketed in the U.S. prior to October 15, 1994?**

   No. Dietary ingredients marketed prior to October 15, 1994 ("pre-DSHEA dietary ingredients") are not NDIs and therefore do not require a NDI notification. See questions IV.A.6 and IV.A.9 for more on how FDA interprets the terms "marketed" and "dietary ingredient" in the definition of a NDI (21 U.S.C. 350b(c)).

3. **Is an ingredient that was used to make a conventional food marketed before October 15, 1994, a NDI if the ingredient was not a dietary ingredient marketed in the U.S. before October 15, 1994?**

   Yes. The use of an ingredient in a conventional food before October 15, 1994 does not determine whether the ingredient is a NDI. What matters is whether the ingredient was marketed as a dietary ingredient -- meaning in or as a dietary supplement, or for use in dietary supplements -- in the U.S. before October 15, 1994. Therefore, an ingredient that was used to make a conventional food before October 15, 1994 is a NDI unless the ingredient was also marketed as a dietary ingredient in the U.S. before October 15, 1994. (See questions IV.A.6 and IV.A.9 for FDA's views on the meaning of "marketing" and "dietary ingredient" in the NDI definition.)

   a. **Is a NDI Notification required for a dietary supplement containing a NDI if the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered?**

      No. Even though an ingredient that was used to make a conventional food before October 15, 1994 is a NDI (unless it was also marketed as a dietary ingredient before that date), a NDI notification is not required for a dietary supplement containing the NDI as long as the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered (21 U.S.C. 350b(a)(1)).

   b. **Does the adulteration standard in 21 U.S.C. 342(f)(1)(B)[7] apply to a dietary supplement containing a NDI for which a NDI notification is not required because the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered?**

      Yes. The adulteration standard in 21 U.S.C. 342(f)(1)(B) applies to all dietary supplements that contain a NDI, even if the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered (see question IV.B.2). See section IV.B for more information about the exception to the NDI notification requirement for certain NDIs that have been present in the food supply as conventional foods.

4. **Is a substance that was a component of a conventional food marketed before October 15, 1994, a NDI if the component was not a dietary ingredient marketed in the U.S. before October 15, 1994?**

   Yes, assuming the component meets the definition of a dietary ingredient. The mere presence of a substance as a component of a conventional food that was marketed before October 15, 1994 does not establish that the substance was marketed as a dietary ingredient before that date. Similarly, the fact that the component may have been isolated as part of an analytical chemical procedure to examine the composition of the previously marketed food before October 15, 1994, is not sufficient to establish that the component is a pre-DSHEA dietary ingredient or even that it is a dietary ingredient at all. If it is not a dietary ingredient, it is ineligible to be a NDI. If the food component fits into one of the dietary ingredient categories (for example, if it is a metabolite or extract of another dietary ingredient) but was not marketed as a dietary ingredient before October 15, 1994, it would be a NDI. (If the substance was also marketed as a dietary ingredient before that date, then it is not a NDI. (See questions IV.A.6 and IV.A.9 for FDA's views on the meaning of "marketing" and "dietary ingredient" in the NDI definition.))

5. **Is a substance that was a component of a dietary supplement marketed before October 15, 1994, a NDI?**

   No, if the substance was a dietary ingredient in the dietary supplement that was marketed before October 15, 1994, then it would not be a NDI. However, there are also two other possibilities about a substance's status if the substance was not a dietary ingredient in the dietary supplement marketed before October 15, 1994. If the substance was present in the pre-DSHEA dietary supplement as a food additive rather than as a dietary ingredient, and does not fit within one of the enumerated categories of dietary ingredients in section 201 (ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)), then it would not be a dietary ingredient that could be used in a dietary supplement. Finally, if the substance was present in the pre-DSHEA dietary supplement as a food additive rather than as a dietary ingredient, but does fit within one of the enumerated categories of dietary ingredients in section 201(ff)(1) of the FD&C Act, then it would be a NDI.

6. **What does "marketing" a dietary ingredient mean?**

   FDA considers "marketing" a dietary ingredient to mean selling or offering the dietary ingredient for sale (1) as a dietary supplement, (2) in bulk as a dietary ingredient for use in dietary supplements, or (3) as an ingredient in a blend or formulation of dietary ingredients for use in dietary supplements. A dietary ingredient may be "marketed" by physically offering the article for sale at a retail establishment, listing it for sale in a catalog or price list, or through advertising or other promotion, if the promotion makes clear that the article is available for purchase. "Coming soon" advertisements would not qualify

7. **Is a dietary ingredient marketed outside the U.S. prior to October 15, 1994, considered to be a NDI if it was not marketed in the U.S. before that date?**

   Yes. Submitting documentation that the ingredient was marketed in any other country before this date does not establish that the ingredient is not a NDI. The only kind of marketing that is relevant to whether a dietary ingredient is a NDI is marketing in the U.S. before October 15, 1994.

8. **What documentation would I need to show that my dietary ingredient was marketed prior to October 15, 1994?**

   Documentation to show that a dietary ingredient is not a NDI should consist of written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994. Examples include sales records, manufacturing records, commercial invoices, magazine advertisements, mail order catalogues, or sales brochures. Documentation should include adequate information to establish that marketing took place in the U.S., the identity (e.g., chemical or botanical name) and form (e.g., ground herb, water extract, oil) of the marketed ingredient, and whether the ingredient was marketed as a dietary ingredient or for some other purpose.

   Affidavits attesting to recollection of historical events which are unsupported by contemporaneously created written records are not adequate to show that an ingredient was marketed prior to October 15, 1994. Even if a person who submits an affidavit attesting to his or her recollection of when a dietary ingredient was first marketed is honestly stating his or her present beliefs, we do not regard such assertions alone, without any sort of objective, verifiable documentation from the time of marketing, as an adequate basis to establish prior marketing of a substance as a dietary supplement.

9. **Is marketing an ingredient for any use prior to October 15, 1994, sufficient to conclude that it is not a NDI?**

   No. The marketing of an ingredient as a conventional food, as a drug, or for any other non-food use cannot be used as evidence that an ingredient is not a NDI. Unless the ingredient was marketed as a dietary ingredient for use in a dietary supplement prior to October 15, 1994, it is a NDI.

10. **Is there an authoritative list of dietary ingredients that were marketed prior to October 15, 1994 (a so-called "grandfathered list" or "old dietary ingredient list")?**

    No. Each supplement manufacturer or distributor is responsible for establishing that the dietary ingredients in its dietary supplements comply with the NDI notification requirements. While some trade associations and other industry groups have published lists of "old dietary ingredients,"[8] these lists have not been verified by FDA and are not backed by evidence that the ingredients listed were actually marketed prior to October 15, 1994. The lists contain ingredients FDA believes are unlikely to have been marketed as dietary ingredients, like acetaminophen or pharmaceutical glaze, and mixtures that are only vaguely described, like "sterol complete premix." The introduction to one trade association list[9] states that the association did not independently verify that the substances on the list were in use before October 15, 1994. The cover page of the list specifically states, "This list is compiled solely for reference purposes and does not constitute verification that any specific dietary ingredient was or was not marketed as a dietary supplement before October 15, 1994." Moreover, the trade association's introduction to the list also states, "There is no definitive list of 'grandfathered' dietary ingredients. The best policy is for any company to maintain its own records confirming long-term use of an ingredient." Therefore, 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. See question IV.A.8 for information on the kinds of proof that FDA does accept.

11. **If I change the manufacturing process for a dietary ingredient that was marketed in the U.S. prior to October 15, 1994, and the changes alter the chemical composition or structure of the ingredient, does that make the ingredient a NDI?**

    Most likely. 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. For example, using a solvent to prepare an extract from a pre-DSHEA dietary ingredient creates a NDI because the final extract contains only a fractionated subset of the constituent substances in the original dietary ingredient. In addition, changes that alter the composition of materials used to make the ingredient, such as using a different part of a plant (e.g., using an extract of plant leaves where the root extract from the same plant is a pre-DSHEA dietary ingredient), would create a NDI.

    Firms planning a manufacturing change are encouraged to consult with FDA on any questions as to whether such a change would create a NDI.

12. **Should I submit a new NDI notification if I change the manufacturing process for a NDI that is the subject of a notification for which I have received an acknowledgment without objection from FDA?**

    Yes, unless the manufacturing change does not change the chemical properties of the dietary ingredient or the specifications needed to describe the ingredient. For example, a change in the manufacturing process for a NDI intended to produce particles in the 1 nm to 100 nm (approximate) nanoscale range may alter the chemical properties of the NDI. If so, the resulting ingredient with different chemical properties would likely not be covered under an existing notification for a related substance manufactured without using nanotechnology and, therefore, would likely require a NDI notification. Manufacturers planning a manufacturing change are encouraged to consult with FDA on any questions as to whether such a change would be viewed as having created a different NDI.

B. **Exception to Notification Requirement for Certain NDIs with a History of Use in Conventional Food**

1. **When is a notification not required for a NDI?**

   A notification is not needed when a dietary supplement product contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food is not chemically altered. See questions IV.B.3 and IV.B.4 for FDA's current thinking on when a food has been "chemically altered."

2. **Am I required to submit a NDI notification for a dietary ingredient that has been listed or affirmed by FDA as generally recognized as safe (GRAS) for direct addition to food, self-affirmed as GRAS for direct addition to food, or approved as a direct food additive in the U.S.?**

   No, as long as the direct food additive or GRAS substance has been used in the food supply and is to be used as a NDI without chemical alteration. If the NDI was legally marketed in the U.S. as an ingredient for use in conventional food, it would qualify under section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) as an ingredient exempt from the notification requirement because it has been present in the food supply as an article used for food in a form in which the food is not chemically altered. Similarly, ingredients marketed in conventional foods outside the U.S. are exempt from the NDI notification requirement. However, as discussed in the following question and answer, the NDI adulteration standard still applies, and voluntary NDI notification may be advisable.

   a. **Does the adulteration standard in 21 U.S.C. 342(f)(1)(B) apply to a NDI that has been listed or affirmed by FDA as GRAS for direct addition to food, self-affirmed as GRAS for direct addition to food, or approved as a direct food additive in the U.S.?**

      Yes. The adulteration standard in section 402(f)(1)(B) of the FD&C Act (21 U.S.C. 342(f)(1)(B)) applies to all NDIs, including NDIs for which a notification to FDA is not required. Therefore, if the ingredient was not marketed as a dietary ingredient in the U.S. before October 15, 1994 (see questions IV.A.6 and IV.A.9), it is a NDI and the adulteration standard for NDIs applies. That is, a supplement containing the NDI is adulterated unless there is adequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury. If the intake level of the NDI resulting from its use under the conditions recommended or suggested in the labeling of the dietary supplement is the same as or lower than the intake level approved in a food additive regulation or specified in a GRAS regulation and overall cumulative intake of the NDI from dietary sources is the same as or lower than the acceptable daily intake (ADI) (see questions VI.C.5 and VI.C.7), FDA is likely to conclude that there is adequate information to provide reasonable assurance of safety. However, the same is not necessarily true if the intake level of the NDI in the dietary supplement is higher than that resulting from conventional food use of the NDI. For example, if an ingredient generally used in microgram quantities to flavor food is placed in a capsule with a serving level of hundreds of milligrams, a safety analysis would be necessary to determine the safety of the much higher intake level. In the absence of adequate information to provide reasonable assurance that the higher intake level of the NDI from its use in supplement form is safe, the dietary supplement product would be adulterated.

      Although a NDI notification is not required in a situation like this, FDA recommends that manufacturers or distributors of this type of dietary supplement product consult with the agency about their basis for concluding that there is adequate information to provide reasonable assurance that the use of the NDI in the dietary supplement will not present a significant or unreasonable risk of illness or injury. FDA has reviewed and intends to continue reviewing voluntarily submitted notifications for NDIs that are exempt from the notification requirement under 21 U.S.C. 350b(a)(1) because they have been present in the food supply as articles used for food in a form in which the food has not been chemically altered.

3. **What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not result in chemical alteration?**

   Minor loss of volatile components, dehydration, lyophilization, milling, and formation of a tincture or a solution in water, a slurry, a powder, or a solid in suspension do not chemically alter an ingredient.[10] Examples:

   - Leaves or roots of a plant consumed as conventional food (e.g., broccoli or carrots) are dried and ground for sale in powder form.
   - A tincture is made by soaking pears in aqueous ethanol. The mixture is then milled and dried into a powder that is placed in a capsule.

4. **What are examples of processes that chemically alter an article of food present in the food supply to create a dietary ingredient?**

   The following are examples of processes that FDA would likely consider to involve chemical alteration.

   - A process which makes or breaks chemical bonds such as hydrolysis or esterification, unless the bonds created by the process are reversed when the ingredient is dissolved in water (e.g., creation of a soluble salt) or during ingestion.
   - Removal of some components of a tincture or solution in water (e.g., by chromatography, distillation or membrane filtration), which changes the chemical composition of the mixture.
   - Use of solvents other than water or aqueous ethanol (tincture) to make an extract. Water and aqueous ethanol are specifically excluded from processes that chemically alter a food in the official legislative history of DSHEA.[11] Other solvents alter the composition of the extract in significantly different ways, usually by extracting different types of constituents than are extracted using water and aqueous ethanol.
   - High temperature baking or cooking of an ingredient that has not previously been baked or cooked, unless the process causes only minor loss of volatile components with no other changes to the chemical composition of the ingredient.
   - Changing the manufacturing method for an ingredient such that the chemical composition is significantly different (e.g., changes that alter the composition of materials used to make the ingredient, use of a different solvent, use of a chromatographic matrix instead of a passive filter).
   - Application of nanotechnology that results in new or altered chemical properties of the ingredient.

- Changing agricultural or fermentation conditions to alter the chemical composition of the ingredient, such as by sprouting garlic or fermenting yeast using a medium containing large amounts of sodium selenite to create large amounts of organic selenium compounds.
- Fermentation using a fermentation medium different from the one used to make conventional foods in the food supply (e.g., use of a defined commercial growth medium to produce a microorganism previously made by fermenting milk into dairy products like yogurt or cheese).
- Use of a botanical ingredient that is at a different life stage than previously used (e.g., making an extract from unripe instead of ripe apples or using the mycelium instead of the fruiting body of a fungus.)

C. **Other Questions About When a NDI Notification is Necessary**

1. **When should I submit separate NDI notifications for supplements that I manufacture or distribute containing the same NDI?**

   It depends. If you have already submitted a NDI notification for a dietary supplement containing a NDI, you need not submit a notification for a different dietary supplement containing the same NDI as long as (1) the daily intake level recommended or suggested in the labeling of the new supplement will be equal to or less than that specified in your prior NDI notification, (2) the new supplement does not have other dietary ingredients that were not included in your original NDI notification, (3) the target populations (e.g., children or pregnant or lactating women) are the same or a subset of the target populations specified in your original notification, (4) all other conditions of use are the same as or more restrictive (e.g., fewer intended uses, shorter duration of use) than the conditions of use described in your prior NDI notification, and (5) FDA did not express safety or other concerns in response to your prior NDI notification.

2. **If another manufacturer or distributor has already submitted a notification for a particular NDI, and I intend to market a dietary supplement containing the same NDI, should I also submit a NDI notification?**

   Yes. Section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)) makes clear that any dietary supplement that contains a NDI is deemed adulterated unless the manufacturer or distributor of the dietary ingredient or the dietary supplement submits a NDI notification at least 75 days before introducing it into interstate commerce. The statute places the obligation for submitting the notification on each manufacturer or distributor. The original notifier conducted its safety evaluation based on the characteristics and intended use of the specific product under review, including the composition and labeling of the dietary supplement that the notifier was proposing to market. Any other manufacturer or distributor who wishes to market its own dietary supplement containing the same NDI should submit a NDI notification to FDA explaining its own basis for concluding that this new product containing the NDI will "reasonably expected to be safe" under the conditions recommended or suggested in the new product's labeling. Manufacturing processes and specifications needed to establish the identity of a NDI are usually trade secrets that are not available in the NDI docket. It should be noted that the original notifier is under no obligation to share with other manufacturers and distributors any trade secrets or confidential commercial information that were part of the basis for a safety conclusion for the original notifier's product.

3. **Should I notify FDA about a microbial ingredient in my dietary supplement?**

   Yes, if it is a NDI that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered (21 U.S.C. 350b(a)(1)). However, not all bacterial microorganisms are dietary ingredients, and a microorganism that is not a dietary ingredient cannot be a NDI. For example, pathogenic species of bacteria, such as *Salmonella* species or *E. coli*, are not dietary ingredients even though they may have been inadvertently present in foods as contaminants. Bacteria that have never been consumed as food are unlikely to be dietary ingredients. A bacterial microorganism is a dietary ingredient if it is a dietary substance (an intentional constituent of food) or otherwise falls within one of the dietary ingredient categories listed in 21 U.S.C. 321(ff)(1). For example, bacteria that are used to produce fermented foods that are eaten without a cooking or pasteurization step (e.g., lactic acid bacteria used to produce cheese or yogurt) could be "dietary substances for use by man to supplement the diet by increasing the total dietary intake," which are defined as dietary ingredients in section 201(ff)(1)(E) of the FD&C Act (21 U.S.C. 321(ff)(1)(E)). FDA does not have a separate regulatory category or definition for dietary ingredients consisting of live or viable microorganisms.

4. **Can you provide a visual aids to help me decide whether I should submit a NDI notification?**

   Yes. The following table illustrates when a NDI notification is required and whether the supplement is governed by the NDI adulteration standard. In addition, **Appendix A** has a decision tree to walk you through the steps of deciding whether to submit a NDI notification.

Definition of New Dietary Ingredient (NDI), Requirement for NDI Notification and Applicability of NDI Adulteration Standard

	New Dietary Ingredient (NDI)	NDI notification required?	NDI adulteration standard[12] applies?
A dietary ingredient that was marketed in the U.S. before October 15, 1994	No	No	No
A dietary ingredient that was NOT marketed in the U.S. before October 15, 1994 AND was present in the food supply as an article used for food which has	Yes	See a) or b)	Yes
a) not been chemically altered	Yes	No	Yes
b) been chemically altered	Yes	Yes	Yes
A dietary ingredient that was NOT marketed in the U.S. before October 15, 1994 AND was NOT present in the food supply as an article used for food.	Yes	Yes	Yes

D. **Additional Issues to Consider Before Submitting a NDI Notification**

1. **Can a contaminant that is found in the food supply be a dietary ingredient?**

No. Although most constituents of conventional foods in the food supply would be "dietary substances" that could be used as dietary ingredients under section 201(ff)(1)(E) of the FD&C Act (21 U.S.C. 321(ff)(1)(E)), contaminants are different from other food constituents. A contaminant of food (like *Salmonella* or lead) is not a dietary substance that qualifies for use as a dietary ingredient in a dietary supplement product even if it is not poisonous (e.g., sterilized *Salmonella*) because contaminants are not intended for ingestion, nor are they considered to be food or part of the food supply. Contaminants are consumed unintentionally and are not "dietary substance [s] for use by man to supplement the diet by increasing the total dietary intake" (21 U.S.C. 321(ff)(1)(E)).

2. **Is a synthetic copy of a constituent or extract of an herb or other botanical a dietary ingredient?**

   No. A synthetic copy of a constituent of a botanical was never part of the botanical and thus cannot be a "constituent" of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(F)).[13] Similarly, a synthetic version of a botanical extract is not an "extract" of a botanical under section 201(ff)(1)(F) because it was not actually extracted from the botanical.

3. **Are food contact substances and other indirect food additives dietary ingredients?**

   Not usually. Although food contact substances and other indirect food additives may be present in the food supply because they migrate into certain foods from packaging or other articles that contact the food, their presence in these foods is merely incidental. An indirect food additive is not a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" (21 U.S.C. 321(ff)(1)(E)) because it is not consumed as a component of the diet, but merely as a byproduct of its use in articles that contact food. However, if an indirect food additive falls under one of the other dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act, it could be a dietary ingredient.

4. **If I alter the chemical structure of a dietary ingredient, is the new substance still a dietary ingredient?**

   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; however, in rare instances, the new substance may independently qualify for one of the dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act. For example, taurine is the end product of the metabolism of the amino acid cysteine. It is thus a metabolite of an amino acid and fits one of the definitions of a dietary ingredient (see 21 U.S.C. 321(ff)(1)(D), (F)). The enzymatic or synthetic processing of cysteine or any other dietary ingredient would be an appropriate method for the manufacture of a metabolite of a dietary ingredient like taurine for use in a dietary supplement.

5. **In what forms may a dietary supplement containing my NDI be sold?**

   The FD&C Act specifically provides for dietary supplements to be in tablet, capsule, powder, softgel, gelcap, or liquid form (21 U.S.C. 321(ff)(2)(A)(i), 350(c)(1)(B)(i)). In addition, the statute permits dietary supplements in other forms as long as the product is intended for ingestion, is not represented as conventional food, and is not represented for use as a sole item of a meal or of the diet (21 U.S.C. 321(ff)(2), 350(c)(1)(B)(ii)).

6. **When FDA reviews a NDI notification, does the agency consider whether the prohibition in section 301(ll) applies to the use of the NDI in a dietary supplement?**

   No. Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(ll)) prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under 21 U.S.C. 355, a biological product licensed under 42 U.S.C. 262, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. When reviewing NDI notifications, FDA's current practice is not to consider whether section 301(ll) or any of its exemptions apply to the NDI. Accordingly, a "no objection" response to a NDI notification should not be construed to be a statement that a dietary supplement containing a NDI, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

7. **Can an ingredient that has not been marketed as a food or as a dietary supplement, but has been approved as a new drug or licensed as a biologic, be used as a NDI in a dietary supplement?**

   No, unless FDA issues a regulation, after notice and comment, finding that the ingredient, when used as or in a dietary supplement, would be lawful under the Act. A regulation of this type may be requested by filing a citizen petition under 21 CFR 10.30, but none has been issued to date. Absent such a regulation, an ingredient that has been approved as a new drug or licensed as a biologic can be a dietary ingredient for use in a dietary supplement if, and only if, prior to such approval or licensing, the ingredient was marketed as a dietary supplement or as a food.

8. **Can I use an ingredient in a dietary supplement if it has been clinically tested as a drug but has not been approved as a drug in the U.S.?**

   It depends on whether the ingredient was authorized for investigation in clinical trials under an investigational new drug application (IND), whether the date the IND went into effect was before or after the date the ingredient was first marketed as a food or as a dietary supplement, whether the clinical trials were "substantial clinical investigations," and whether their existence was made public. The general rule is that an article that has been authorized for investigation as a new drug or as a biologic before being marketed as a food or as a dietary supplement cannot be marketed as a dietary supplement if substantial clinical investigations of the article have begun and the existence of such investigations has been made public. FDA can create an exception to this prohibition by regulation, but only if the agency finds that the use of the article in dietary supplements would be lawful. To date, no such regulations have been issued. The appropriate mechanism to request such a regulation is to file a citizen petition under 21 CFR 10.30.

9. **How do I determine whether a dietary ingredient is an article that is approved or authorized for investigation as a new drug?**

   Either an entire product or a component of the product, such as an active ingredient, may be "an article that is approved as a new drug" or an article "authorized for investigation as a new drug" within the meaning of section 201(ff)(3)(B) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)).[14] For example, assume that Substance A, which is a constituent of a plant and has never been marketed as an article of food or as a dietary supplement, is a botanical dietary ingredient under section 201(ff)(1)(C) of the FD&C Act. A drug company is studying a salt of Substance A, "Substance A hydrochloride," as an investigational new drug under an IND. In this situation, the relevant article for purposes of whether Substance A can be used in a dietary supplement is not Substance A hydrochloride, but Substance A itself, because Substance A is the active moiety[15]that is being studied for its possible therapeutic action. Any compound that delivers Substance A is

excluded from being used in a dietary supplement.[16]

10. **Can a dietary ingredient that was authorized for investigation as a new drug in the past become a NDI if the IND was withdrawn or the ingredient is no longer being studied?**

    It depends on the facts of the particular situation (see answer to IV.D.8 above), but withdrawal of the IND and cessation of clinical trials of the ingredient make no difference in whether the ingredient may be used in a dietary supplement. The dietary supplement category does not include an article authorized for investigation as a new drug or biologic for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such authorization marketed as a dietary supplement or as a food, unless FDA has issued a regulation finding that the article would be lawful under the Act (21 U.S.C. 321(ff)((3)(B)(ii)). "Authorized for investigation" means that the article is the subject of an IND that has gone into effect (see 21 CFR 312.40).

11. **Can I manufacture and sell a dietary supplement containing a dietary ingredient that was marketed as a food or dietary supplement before it was approved as a drug, licensed as a biologic, or authorized for investigation under an IND?**

    Yes, in this situation the dietary ingredient may be used in dietary supplements. In considering whether a substance has been "marketed as a dietary supplement or as a food," FDA looks for evidence of one of the following:

    1. Evidence that the substance itself was sold or offered for sale in the U.S. as a dietary supplement, dietary ingredient for use in dietary supplements, or conventional food. For example, a catalog listing a product identified as a "Substance A supplement" would establish the marketing of Substance A as a dietary supplement. Similarly, business records documenting that a substance was offered for sale or sold as an ingredient for use in manufacturing a conventional food would establish the marketing of the substance as a food.

    2. Evidence that the substance was a component of a food or dietary supplement that was sold or offered for sale in the U.S., and that a manufacturer or distributor of the food or dietary supplement marketed it for the content of the substance by, for example, making claims about the substance or otherwise highlighting its presence in the product.[17] For example, in *Pharmanex v. Shalala*, the firm marketed lovastatin, a component of its red yeast rice product Cholestin, by promoting the lovastatin content of Cholestin.[18] Merely showing that the substance was present in a food as a component would not be enough to show that the substance was "marketed," however.

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V. NDI Notification Procedures and Timeframes

A. Procedure for Submitting a NDI notification

1. **Who is required to submit a NDI notification?**

   Either the manufacturer or distributor of a dietary supplement that contains a NDI, or the manufacturer or distributor of the NDI, must notify FDA at least 75 days before the dietary supplement containing the NDI is marketed in the U.S., unless the NDI has been present in the food supply as an article used for food in a form in which the food has not been chemically altered (21 U.S.C. 350b(a); 21 CFR 190.6(a)). Although FDA does review notifications from manufacturers or distributors of NDIs, notifications from ingredient manufacturers do not eliminate the requirement for a notification from the manufacturer or distributor of the dietary supplement in which the NDI will be used unless the prior notification for the NDI (1) included a description of the dietary supplement with the information required by 21 CFR 190.6(b), and (2) provided the history of use or other evidence of safety on the basis of which the notifier concluded that the dietary supplement would reasonably be expected to be safe under its labeled conditions of use.

2. **What should be included in a NDI notification and how should it be presented?**

   The required elements of a NDI notification are listed in 21 CFR 190.6(b). FDA's recommendations for additional information to include are provided in the template below.

   The NDI notification should be well organized to facilitate an efficient and timely FDA review. FDA recommends that the notification be organized by sections, with continuous and consecutive pagination throughout the notification. Each subject area should begin with a new page to facilitate division of the notification among reviewers. The page number should appear in the same general location on every page.
   If you would prefer to use a form to submit your notification, **Appendix B** of this guidance contains a non-fillable sample of the fillable PDF form that you can use. Appendix B also contains a link to the fillable version of the PDF form. The form provides a checklist of the information FDA finds most useful in evaluating notifications and organizes the information in a format consistent with the agency's current electronic review system. Although the format of the form and template differ slightly, either will help you produce a well-organized notification that meets FDA's content recommendations

   Recommended Template for Organizing a NDI Notification

   I. **Cover Letter**

   Consumer Safety Officer
   Office of Nutrition, Labeling and Dietary Supplements (HFS-810)
   Center for Food Safety and Applied Nutrition
   Food and Drug Administration
   Department of Health and Human Services
   5100 Paint Branch Parkway
   College Park, MD 20740

   DEAR SIR OR MADAM:

The undersigned, _____, (*Name of the primary contact person designated by the manufacturer or distributor that is submitting the notification*) submits this NDI notification under section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act with respect to _____(*Name of the dietary supplement containing the new dietary ingredient*), which contains the following new dietary ingredient: _____. _____ . [*For herbs and other botanicals, the name should include the Latin binomial name, including the author citation.*]

Additional information necessary to uniquely characterize the new dietary ingredient:
_____

- *If the new dietary ingredient is a botanical or is derived from a botanical, the plant part of the botanical that is the source of the new dietary ingredient should be indicated.*
- *Examples of information sufficient to uniquely characterize a new dietary ingredient that is a single molecular entity could include the common or usual name of the molecular entity, the chemical identity, the chemical structural formula as noted in ChemIDPlus Advanced, PubChem, or International Union of Pure and Applied Chemistry (IUPAC), and the Chemical Abstracts Service (CAS) registry number (if available).*
- *NDIs consisting of more than one molecule should be described in a way that accurately communicates the basic nature of the ingredient and its characterizing ingredients or components. Examples:*
  - *Bacteria should be described by Latin binomial name and strain designation.*
  - *Unusual forms of botanicals should be identified (e.g., immature apples or malted barley.)*
  - *If a botanical is grown or cultured to incorporate an unusual constituent (e.g., selenium yeast),that fact should be disclosed.*
- *If the NDI was the subject of a previous NDI notification submitted by you or by the manufacturer or distributor from which you obtain the NDI, please include the docket report number, which you can find in FDA's letter responding to the notification.*

_____

(Signature of the contact person designated by the manufacturer or distributor of the dietary supplement that contains the new dietary ingredient) [*This signature is required by 21 CFR 190.6 and should be the primary contact, i.e., the person who represents the notifier in any discussions with FDA and who designates any additional contact persons in the notification or in subsequent correspondence.*]

Primary Contact:

(*Typed or printed name, title, address, telephone number and, if available, email address and facsimile number of the primary contact person.*)

Additional Contacts:

(*Typed or printed name, title, address, telephone number and, if available, email address and facsimile number of each additional contact person.*)

Contact persons can be agents, employees, officers, consultants or attorneys.

II. **Table of Contents**

The table of contents should consist of a listing of the sections of the notification in the order in which they appear, along with the beginning page number of each section. Each section of the notification should begin with a new page.

III. **Body of the Notification**

A. **Administrative**

1. Description of the NDI, the dietary supplement containing the NDI, and the conditions of use of the dietary supplement (see question VI.A.19).
2. Identification of information believed to be trade secret or confidential commercial information, including the basis for identifying the information as such (see question V.B.16)
3. Safety Narrative for the dietary supplement (see question VI.C.3)

B. **Attachments used to establish identity**

[*Provide only the information that identifies your NDI and dietary supplement. Do not provide efficacy data unless it is included in references that also provide identity information.*]

1. Detailed description of the identity of the new dietary ingredient and the dietary supplement.
2. Manufacturing methods and practices to establish identity and safety
3. Specifications to identify dietary ingredients, other ingredients, and contaminants, including the analytical methods used to establish each.
4. Identity References

   This subsection should contain reprints or photocopies of the full text of all published and unpublished identity

references that have not already been included in other subsections of the Identity section.

C. **Safety and Toxicology Attachments**

[*Provide only the information that formed the basis for your conclusion that the dietary supplement containing the new dietary ingredient is reasonably expected to be safe. Do not provide efficacy data unless it is included in studies that also provided safety information.*]

1. Comprehensive Safety Profile for the NDI (see question VI.C.2).
2. Toxicology Studies
3. Human Studies
4. Other Studies
5. History of Use
6. Other Evidence of Safety
7. Other Safety and Toxicology References
   This subsection should contain reprints or photocopies of the full text of all published and unpublished safety and toxicology references that have not already been included in other subsections of the Safety and Toxicology section.

IV. **Complete List of References**

3. **How should the notification describe the NDI?**

Your notification should include (1) a statement that indicates what category of dietary ingredient, as defined in section 201(ff)(1)(A)-(F) of the FD&C Act, describes the NDI, and that explains the basis for this conclusion; (2) a description of the manufacturing process used to make the NDI, including process controls; (3) a description of the physical properties and chemical composition of the NDI; (4) a specification sheet that describes the critical safety attributes of the NDI, including the purity and strength of the NDI and the levels and identities of any impurities and contaminants. See section VI.A for further information.

4. **How should the notification describe the dietary supplement in which the NDI will be used?**

The notification should contain a description of the dietary supplement in which the NDI will be used, including (1) the level of the NDI in the dietary supplement; (2) the identity and level of any other dietary ingredients and non-dietary ingredients (e.g., excipients and fillers) in the dietary supplement; (3) a description of the manufacturing process of the dietary supplement, including process controls; (4) a specification sheet for the dietary supplement that describes its critical safety attributes; (5) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, a discussion of the ordinary conditions of use of the dietary supplement. The conditions of use should include the serving form (e.g., tablet, capsule, powder, etc.), serving size (e.g., weight or volumetric measure), number of servings per day, serving instructions, duration of use, target population, and excluded populations (if any). For purposes of review, the highest described serving size and number of servings with a duration of daily lifetime use by all age groups and other populations will be assumed, unless the notification specifies otherwise.

5. **What information should <u>not</u> be in the NDI notification?**

The notification should only contain data or information, as described in the safety narrative or comprehensive safety profile, that helps provide a basis for the safety of the NDI or the dietary supplement in which the NDI will be used. It should not contain general or extraneous information. For example, data or information that is used primarily to substantiate a claim about the efficacy of the ingredient or supplement is not useful unless it also contains information that pertains to safety. In addition, the requirement to notify FDA within 30 days after marketing a supplement with a labeling claim described in section 403(r)(6) of the FD&C Act (21 U.S.C. 343(r)(6)) cannot be met by submitting the required information in a pre-market NDI notification.[19] Published review articles and publications and websites that promote other products should not be included unless the information in the articles or websites can be specifically linked to the NDI or dietary supplement that is the subject of the notification.

6. **Should I explain how the information in the notification provides a basis to conclude that the dietary supplement in which the NDI will be used will reasonably be expected to be safe?**

Your notification should include a dietary supplement Safety Narrative containing your objective evaluation of the history of use or other evidence of safety cited in the notification, along with an explanation of how the evidence of safety provides a basis to conclude that the dietary supplement containing the new dietary ingredient, when used under the conditions described in the notification, will reasonably be expected to be safe. See question VI.C.3 for further information.

7. **Does FDA have a form for NDI notifications, and, if so, do I have to use it?**

Yes, Appendix B of this guidance contains a NDI notification form in PDF format, but use of the form is not required. FDA recommends the use of the form because it provides a checklist of the information FDA finds most useful in evaluating notifications and organizes the information in a format consistent with the agency's current electronic review system.

At the present time, FDA is not able to accept NDI notifications electronically, but we are making plans to convert to an electronic submission system for NDI notifications. If you use the NDI notification form in Appendix B, you can fill it out on your computer, but you must then print it out and mail it or deliver it to FDA along with your references and other attachments (21 CFR 190.6(a)).

The format of the NDI notification form is slightly different from the format described in the template in question V.A.2, above. For example, the form functions as a table of contents for the notification and contains fillable fields for conditions of use and contact information. Either format will help you produce a well-organized notification that meets FDA's content recommendations.

8. **When should a NDI notification be submitted?**

You must submit your NDI notification at least 75 days before you introduce or deliver for introduction into interstate commerce a dietary supplement that contains a NDI for which a notification is required (i.e., a NDI that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered) (21 U.S.C. 350b(a); 21 CFR 190.6(a)).

9. **How many copies of a NDI notification should be submitted?**

   You should submit an original and one copy of the NDI notification. Although the regulation requires two copies to be submitted (see 21 CFR 190.6(a)), FDA no longer needs the second copy and does not intend to enforce that part of the requirement. The original must be a paper document, as the regulation does not provide for electronic submissions. For the required copy, FDA accepts either paper or an exact copy of the original scanned into an electronic file in PDF format on a CD-ROM disk.

10. **Where should a NDI notification be submitted?**

    Submit your NDI notification to: Consumer Safety Officer, Office of Nutrition, Labeling and Dietary Supplements (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740.

11. **How should published literature and other scientific information cited in the notification be listed?**

    The notification should include a table of contents with a reference section at the end of the notification (see suggested table of contents format in question V.A.2). The reference section should list all studies and publications cited in the notification, including reference numbers or descriptors used to cite each study or publication in the body of the notification. The list of references should include unpublished work as well as publications.

12. **How should unpublished scientific work be described?**

    The more complete the description of the data and methods in an unpublished study report, the more easily FDA reviewers will be able to evaluate whether the data support the safe use of the dietary supplement containing the NDI. Abstracts or cursory summaries of data (e.g., "a 90-day study in 5 rats failed to show any toxicity") do not provide enough detail to be useful as a basis for a safety determination.

13. **Do I have to provide copies of publications cited in the notification to FDA?**

    Yes. All references to published information offered in support of the notification must be accompanied by reprints or photocopies of such references (21 CFR 190.6(b)(4)). You should not submit only the abstract or bibliographic citation of any publication or other material with your notification; instead, submit a photocopy or reprint of the full text. Do not submit abstracts that are the only published report of a scholarly or scientific work (21 CFR 190.6(b)(4)). Because abstracts do not contain sufficient information to judge the reliability of the scientific conclusions drawn in the study and generally do not undergo the rigorous review and editing used to evaluate other publications, they do not provide data that are useful in evaluating the safety of a NDI.

14. **May I use material published in languages other than English to support the safe use of my NDI?**

    Yes, material written in a foreign language may be used as part of the basis for a conclusion that the NDI will reasonably be expected to be safe under the conditions of its intended use in the dietary supplement; however, the material must be accompanied by an accurate and complete English translation (21 CFR 190.6(b)(4)).

15. **Should raw data be provided?**

    The level of detail that should be provided (raw data vs. summary) depends on how important the data in question are to the conclusion of safety and also whether the data suggest a safety problem. The more critical the data are to the overall evaluation, the more detail is needed. Data summaries (e.g. a table containing the average value and range or standard deviation for each parameter measured in a safety study or the peaks in a spectrum or chromatogram) are usually sufficient unless the data suggest that some values are outside of the acceptable range, in which case the individual values (raw data) should be provided. During review of the notification, FDA may request submission of raw data or other additional information. If the additional information is a substantial amendment, FDA will reset the filing date and start a new 75-day review period.

16. **How should I identify information that I believe is trade secret or confidential commercial information?**

    As provided for in 21 U.S.C. 350b(a)(2) and 21 CFR 190.6(e), after the 90th day after the filing date of the notification, all information in the notification will be placed on public display, except for any information that is trade secret or confidential commercial information (CCI).

    FDA recommends that you clearly identify any information in the notification that you believe is trade secret or CCI -- either by marking the information where it appears in the notification or identifying this information in a separate document that accompanies the notification -- and that you provide an explanation for the basis for this belief. Likewise, if you believe there is no trade secret or CCI contained in the notification, FDA requests that you state this in your notification.

    Trade secret information is 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. There must be a direct relationship between the trade secret and the productive process; for example, information relating to the manufacturing process (21 CFR 20.61(a)). Examples of trade secret information might include manufacturing methods and the product composition (if different from what is declared on the label), product specifications needed to protect proprietary composition information (including proprietary analytical methods used to evaluate the product), and certificates of analysis.

    Confidential commercial information covers information that is related to a business or trade and is "confidential" (21 CFR 20.61(b)). In the case of information that FDA requires to be submitted, such as a NDI notification, the information is "confidential" if its disclosure is likely to cause substantial harm to the competitive position of the submitter.[20] Examples of confidential commercial information might include sales statistics, dollar volume, amount or source of income (e.g., a company's list of customers), profits or losses, expenditures (of any person, firm, partnership, corporation or association), name of suppliers or subcontractors, or brand of equipment.

    FDA believes that the following data and information contained in a notification are generally not trade secrets or CCI, and therefore would be available for public disclosure after the 90th day after receipt of the notification by FDA:

1. (1) Information about the history of use or other safety information related to the dietary ingredient, including both published and unpublished studies.

2. (2) All correspondence and written summaries of oral discussions relating to the notification, except specific information that is exempt for disclosure under 21 CFR 20.61.

17. **What signature and contact information should I provide?**

The signature of the person designated by the notifier is required by 21 CFR 190.6(b)(5). This person should be the primary contact, who represents the notifier in any discussions with FDA and who designates any additional contact persons in the notification or in subsequent correspondence. The typed or printed name, title, address, telephone number and, if available, email address and facsimile number of the primary contact person should be listed at the end of the cover letter that accompanies the notification (see suggested notification format in question V.A.2) so that FDA can reach him or her when necessary. The typed or printed name, title, address, telephone number and, if available, email address and facsimile numbers of additional contact persons for the notification should be listed after the contact information for the primary contact. Contact persons can be agents, employees, officers, consultants or attorneys for the notifier.

B. **What Happens After a NDI Notification is Submitted?**

1. **When is a NDI notification considered to be filed?**

The date when FDA receives a complete notification is the date of filing. A complete notification is a notification that contains all the information required by 21 CFR 190.6. The date of filing is the start of the 75-day premarket review period during which a dietary supplement product containing the NDI that is the subject of the notification may not be marketed (21 U.S.C. 350b(a)(2); 21 CFR 190.6 (c)). If the notification does not meet the requirements of 21 CFR 190.6, a member of FDA's New Dietary Ingredient Review Team will contact the notifier to determine how long it will take for the notifier to provide the missing information. If the notifier can provide the information within 14 days, FDA will file the notification upon receipt of the missing information. If the notifier cannot provide the missing information within 14 days, FDA will consider the notification incomplete and will mail a letter so informing the notifier. Upon request, members of the New Dietary Ingredient Review Team will provide guidance on how to produce a notification that meets the requirements of 21 CFR 190.6.

2. **What are examples of omissions that cause a notification to be incomplete?**

An incomplete notification does not satisfy the notification requirement found in section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)), and therefore, if the dietary supplement containing the NDI is marketed, it is deemed to be adulterated under section 402(f) of the FD&C Act (21 U.S.C. 342(f)) unless the notifier has amended the notification to supply the missing information at least 75 days before the dietary supplement is introduced or delivered for introduction into interstate commerce (21 U.S.C. 350b(a)). FDA does not evaluate safety or identity information in incomplete NDI notifications. The following are examples of omissions that make a notification incomplete:

- Material in a language other than English that is either not translated or is translated inaccurately.
- Citations to published literature for which a full copy of the publication is not provided.
- A notification that is not signed or contact information that is inaccurate and does not permit FDA to establish contact with the notifier.
- Receipt of a copy of the notification that is not a duplicate of the original.

3. **What type of response may I expect to receive from FDA and when?**

Within 75 days after FDA files your notification, you may expect a letter acknowledging receipt of the notification and stating the date on which the notification was filed. Examples of the types of response letters FDA commonly sends include, but are not limited to: (1) letter of acknowledgement without objection; (2) letter listing deficiencies that make the notification incomplete under 21 CFR 190.6; (3) objection letter raising safety concerns based on information in the notification or identifying gaps in the history of use or other evidence of safety; and (4) letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient under 21 U.S.C. 321(ff)(1), or the product is excluded from the definition of "dietary supplement" under 21 U.S.C. 321(ff)(2) because it is not intended for ingestion). The letter may contain information about the agency's review of your notification, and it may ask you to submit additional information if your notification is incomplete or raises safety questions. The letter also contains a report number which identifies the notification in the FDA docket. If you provide FDA with a facsimile number in your notification, FDA will send a facsimile of the response letter to that number on the day that the response letter is mailed.

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VI. What to Include in a NDI Notification

A. **Identity Information About the NDI and the Dietary Supplement**

1. **What is the purpose of including information about the identity of the NDI and the dietary supplement containing the NDI in a notification?**

The purpose of including identity information in the notification is to establish what the NDI is, including the category of dietary ingredient in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)) to which it belongs; to identify the other ingredients and components of the dietary supplement; and to provide the basis for FDA to evaluate the qualitative and quantitative relationship between the ingredients in the dietary supplement and the substances that are described in the history of use or other evidence of safety provided in your notification. Without this information, FDA cannot evaluate whether there is a history of use or other evidence establishing that the dietary supplement containing the NDI will reasonably be expected to be safe under your proposed conditions of use.

2. **What types of identity information should I include in my NDI notification?**

You should describe the manufacturing process, the physical and chemical composition of the NDI, controls for batch-to-batch variability, as well as the identity and level of any impurities and contaminants that may be in the NDI. FDA recommends that you establish identity specifications for the NDI and for those components of the NDI or dietary supplement that are relevant to establishing the basis for the safety of the dietary supplement. You should describe these specifications in your notification as recommended in question VI.A.4, below.

3. **How much detail should my description of the manufacturing process contain?**

The description should have sufficient detail to enable FDA to understand the overall process used to make the NDI and the dietary supplement. You should identify any points in the process that you know to be relevant to the safety of the dietary supplement. Detailed descriptions of manufacturing can be limited to those portions relevant to safety, if they can be identified. For example, you might establish a specification to limit mold contamination of a component used to make your NDI (e.g., aflatoxin in corn). You might also use a specification for the temperature of a key extraction step to prevent formation of a toxic byproduct and/or a specification for that byproduct in an analysis of an interim material or of the final product. You may describe the entire process and all specifications or select only those that are relevant to the identity and safety information that provides the basis for the safety of your NDI.

4. **What is a specification?**

A specification is a set of standards developed by the manufacturer or distributor of a material (e.g., a NDI or a dietary supplement). The specification includes standards for each of the components of the material, and for the material as a whole. For the purpose of a NDI notification, the specification should include critical safety attributes, and may omit attributes not relevant to safety or identity. The specification sheet should provide a list of tests, the acceptance criteria for each test, and analytical methods used to support the acceptance criteria. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. They are used to determine whether to accept or reject the ingredient or product being analyzed. Acceptance criteria should be explicit, rather than vague.

The description of the analytical methods should include a detailed set of directions that must be followed exactly for the results to be accepted for the stated purpose. The directions should cover all steps from preparation of the test sample to reporting the results of the analysis. The description of the method should be complete, whether it is proprietary or included as a publication. Details of the method, such as a description of the chromatographic column, solvent elution conditions, and the source and authenticity of any reference standards, are integral to understanding how a method is used to identify the analyte.

A vague acceptance criterion is rarely useful. For example, it is not informative to say that a chromatogram or a spectrum "matches the reference sample" unless every peak matches (both height and location) or there is a description of which peak or peaks match and how they match (e.g. description of the acceptable variation in peak retention time and peak height or area under curve). The use of "fingerprint" analysis of complex spectra or chromatography of mixtures containing many ingredients does not require knowledge of the identity of all or even any of the peaks, but does require matching sufficient numbers of peaks across the entire spectrum or chromatogram to assure the validity of the test result. Components that are known to be toxic can be identified by a single acceptance criterion (e.g. "less than"), but acceptance criteria for other components should be expressed as a range. The source and authenticity of analytical standards should also be documented.

5. **What specifications for my process and ingredients should I include in the notification?**

As a manufacturer or distributor of a dietary supplement, you must establish specifications for the components of your product, including:

- an identity specification for each component;
- component specifications necessary to ensure that specifications for the purity, strength and composition of dietary supplements manufactured using the components are met; and
- limits on the types of contamination that may adulterate or may lead to adulteration of the finished product (21 CFR 111.70).

You should describe in your notification those specifications that are relevant to the identity of the NDI and to the safe consumption of your dietary supplement product. You should also list and explain the role of those specifications that establish the identity of the NDI and are relevant to the safe use of your dietary supplement, including how you arrived at the criteria for acceptance or rejection based on the results of each test in the specification. This might include specifications for starting materials used to make your NDI, process controls during manufacturing, or interim or final product specifications for the NDI or the dietary supplement. You should describe the controls in place to maintain the strength, composition and purity of the NDI throughout the shelf life of the product. If you rely on history of use or other evidence of safety for materials other than your NDI, you should explain, based on the manufacturing method and specifications for your NDI, the qualitative and quantitative relationship between your NDI and the materials used to demonstrate safety. For example, if your NDI is a mixture of polyphenolic compounds extracted from grapes, you might use information such as quantitative HPLC analyses to relate the quantity of those compounds in a serving of your ingredient to the quantity in a serving of unprocessed grapes or grape juice.

Table 1. An Example of a Specification Sheet or Table for a Dietary Ingredient

Test	Acceptance criteria	Analytical Method (Referenced Method or In-House Method Name)
Appearance: Color/physical state	White to off white/powder	Visual, R-01545[1]
Dietary ingredient identity	Matches reference standard	HPLC, R-02030[1]
Dietary ingredient assay	a ± b mg/capsule	HPLC, R-02030[1]
Related substances: Total related substances	No more than (NMT) 0.5% of total peak area of the dietary ingredient	HPLC, R-02030[1]
Microbial limits, if applicable: Total Aerobic Microbial Count *Staphylococcus aureus Pseudonomas aeruginosa*	NMT 100 CFU/g Absent Absent	USP <61>
Apparent pH, 25 °C (if applicable)	4.5 to 5.5	USP <791> or in house method

Residual solvent, e.g., Ethanol, acetone, hexane.[2]	NMT specified limit in ppm	GC, R-01901[1]
Heavy metals	NMT 20 ppm	USP 30<231> Method II

[1] In-house analytical methods, which must be described in sufficient detail in the NDI notification for FDA to evaluate them. Use of a method published by an authoritative source (such as AOAC or USP) or described in a peer reviewed journal (such as *Journal of Chromatography)* is also appropriate, as long as a reprint or copy of the publication is provided).

[2] Solvents that were used in the manufacturing process.

6. **What additional information should I submit if my ingredient is a discrete chemical entity (e.g., a vitamin, mineral, amino acid, or a constituent or a metabolite of another dietary ingredient)?**

   You should provide sufficient information to uniquely characterize your ingredient as a discrete molecular entity (or mixture of discrete molecular entities). Information that uniquely characterizes a single molecular entity should include the common or usual name of the molecular entity, the molecular formula and formula weight, the structural formula (as noted, for example, in ChemIDPlusAdvanced, PubChem, or International Union of Pure and Applied Chemistry (IUPAC)), and, if available, the Chemical Abstracts Service (CAS) registry number. For example, if the substance exists as a configurational isomer (stereoisomer), such as an enantiomer, or a geometric isomer, the isomer in question should be specified and characterized. For an enantiomer, the notification should include the correct stereoisomeric structure and the correct chemical name with the appropriate R or S designations. Other systems of nomenclature (such as D or L for amino acids) are also appropriate as long as the name unambiguously identifies which isomer(s) are present. For a geometric isomer, the correct cis (Z) or trans (E) stereoisomeric structure and the correct chemical name should be provided. In addition, if the notification asserts that the NDI is a metabolite, you should document the basis for this assertion. For example, the notification should cite evidence showing that the level of the NDI in the human body increases with intake of a precursor constituent of food. (See definition of "metabolite" in Section VII.)

   Other relevant information might include:

   - Specifications for your raw materials (e.g., food grade), and evidence that your raw materials conform to the specifications.
   - A detailed description of each step of the production process, including
     - Reaction conditions in the synthesis and purification process.
     - The process and quality controls used in the manufacturing process; for example, temperature, time, pH, shielding gas, etc.
     - Flow diagrams of the manufacturing process.
     - Composition: Provide the identity and quantity (including units and any ranges) for each component.
     - A description of how undesirable byproducts of manufacturing are removed. Undesirable byproducts include unreacted chemical reagents, reaction byproducts, and solvents like methanol or hexane.

7. **What additional chemistry information should I submit if my ingredient is a salt?**

   You should describe the extent to which the salt will dissociate following ingestion, particularly if the history of use or other evidence of safety describes forms of the ingredient other than the salt that is the subject of the notification. Specific discussion of whether different salt forms have different toxic properties also should be included.

8. **What additional chemistry information should I submit if my ingredient is a covalently modified derivative of a dietary ingredient?**

   Covalent modification alters the identity of the ingredient. Examples include covalent bonding of one dietary ingredient to another or exchanging a functional group (e.g. an alcohol) for another (e.g. an acid or an ester). The chemical structure of the new ingredient should be described explicitly and clearly. Before submitting a NDI notification for the new ingredient, you should consider whether it qualifies as a dietary ingredient under one of the categories in section 201(ff)(1)(A)-(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(A)-(F)). If not, the new ingredient cannot be a NDI because it is not a dietary ingredient.

9. **What information should I submit if there is a history of use or other evidence of safety for a substance or product that is similar to, but not exactly the same as, my NDI or dietary supplement?**

   You should use chemical, microbiological, and botanical characterizations, as appropriate, to explain how the substance or product is similar to your NDI or dietary supplement and to provide a rationale for how the safety information that is presented for the similar substance or product is relevant to the safety of your NDI or dietary supplement. Note that developing such a rationale requires knowledge of the identity (e.g., composition and strength) of the related substances that were studied or that have a history of safe use. The discussion in the notification should include the scientific rationale that supports extrapolating conclusions from a safety evaluation of the related substance or product to your NDI or dietary supplement. Otherwise, such evidence of safety may not provide a basis to conclude that your NDI or product will reasonably be expected to be safe.

10. **What additional identity information should I submit if my product contains a mixture of ingredients?**

    You should state the identity and level of each ingredient in the dietary supplement, including both dietary ingredients and other ingredients, such as those used for a technical or functional effect in the product, including binders, fillers, and color additives. You should also describe how the combination of all the ingredients in the mixture relates to the history of safe use or other evidence of safety of the dietary supplement in which the NDI will be used. The dietary supplement Safety Narrative should address bioavailability of the ingredients as formulated, including use of any excipients that affect bioavailability of any of the dietary ingredients in the dietary supplement.

11. **What identity information should I submit if my NDI is a botanical or is derived from a botanical?**

You must provide the Latin binomial name, including the author citation, for any ingredient that is a botanical or derived from a botanical (21 CFR 190.6(b)(2); see also 21 CFR 101.4(h)). We recommend that you also specify the part of the plant from which the ingredient is derived. You may, in addition, provide a common or usual name for your botanical ingredient. The Latin binomial name should be in accordance with internationally accepted rules on nomenclature, such as those found in the International Code of Botanical Nomenclature (ICBN). FDA recommends use of the most recent edition of ICBN.[21]

12. **What information should I submit to describe a botanical NDI or a NDI derived from a botanical?**

You should provide the following:

- Properly prepared and curated vouchers of the botanical source material;
- Conditions of propagation, if they involve deliberate manipulation of propagation in a manner that is significantly different than common plant propagation and breeding practices;
- Geographic origin of cultivated or wild harvested plant material;
- Conditions of cultivation (e.g., wild harvest, field, or greenhouse);
- Period during which the botanical is cultivated and harvested (season or month and year); and
- Part of the plant from which the ingredient is derived.

13. **Should I describe the production methods for my botanical NDI?**

Yes. You should describe the production methods for your botanical NDI to the extent necessary to demonstrate that it is the same as or similar to the botanical materials described in information submitted as evidence of the safety of the NDI. Thus, cultivation of plants or fungi in wild or standard conditions might not require extensive explanation. However, unusual production conditions should be explained. For instance, if you culture *Saccharomyces cerevisiae* in a medium with unusually large amounts of selenium, you should describe the fermentation process, as well as the levels and types of selenium compounds in your final product. If you use traditional or molecular methods to produce a variety with novel properties, you should describe the variety in sufficient detail to demonstrate that the ingredient you derive from it is reasonably likely to be safe under the conditions of use of the dietary supplement to which the NDI will be added.

14. **How should the identity section of my NDI notification deal with toxins in related plants or microorganisms?**

You should identify the toxins or classes of toxins or other deleterious constituents or properties (e.g., antibiotic resistance genes in microorganisms or toxigenic properties for which the toxin is unidentified) known to be present in the same species or in a family or genus that is phylogenetically related to the NDI. You should also document the absence (or the amount, if present) of those toxins or other deleterious constituents or properties in the NDI, as well as in the substances that are the subject of the history of use or other evidence of safety presented in the notification. Identification below the species level (e.g., plant variety or strain designation) can be relevant to the safety determination when some varieties or strains of a species are known to contain toxins.

15. **How should I describe an extract or concentrate of a botanical or a dietary substance?**

You should include the following in the description of your extract or concentrate:

- Overview of the manufacturing process, including a general description of each process step (e.g., a flow chart), followed by a description of the method of manufacturing in sufficient detail to make clear the identity of the final product (the finished extract or concentrate) and how it is similar to and different from the starting material.
- Description and amount, expressed as a percentage or range of percentages, of all added ingredients, including all solvents used, along with specifications for residual solvents other than water in the finished NDI or dietary supplement.
- Concentration or dilution ratio, or range of concentration or dilution ratios, of the finished extract or concentrate relative to the original starting material. If the concentration or dilution ratio is based on the weight of fresh herb, rather than dried, this fact should be disclosed.
- Content, minimum content, or range of content of any marker substances, expressed as a percentage of the finished extract or concentrate, accompanied by (1) a description of whether the marker is a marker of efficacy, toxicity or a surrogate marker, and (2) a calculation or estimate of the relative level of each marker in the NDI compared to the original starting material.
- How the extract or concentrate is standardized from batch to batch and how adulterants such as non-food solvents, pesticides, heavy metals, and filth are excluded.
- If reagents used during processing are likely to make covalent changes to components in the mixture during processing, you should determine whether the new material is still a dietary ingredient. For example, use of a large amount of a strong oxidizing acid like sulfuric acid to process a botanical mixture may create a new "semi-synthetic" mixture that is no longer a mixture of components that were present in the original plant. Therefore, the mixture would no longer be a dietary ingredient.

16. **What additional information should I include if my ingredient is produced using fermentation?**

The notification should include information about the organism(s) and fermentation process used to culture the microorganism that produces the NDI. The safety of the fermenting organism for use in food production should be discussed. Poorly defined microbiological mixtures are acceptable if there is a long history of use in production of food (e.g., mixtures used to make dairy products like kefir or cheese) and the fermentation substrate is consistent with that history of use. The notification should describe the history of use of the fermenting organism(s) to produce food or, in the absence of such history, should thoroughly explain how the manufacturing process excludes toxins and other undesirable byproducts of fermentation from the finished NDI.

The information about the fermentation process should describe the complete media formulation, the fermentation vessel(s), the fermentation conditions, the methods used to harvest the NDI from the fermentation mixture, and any specifications for the production organism in the finished NDI, particularly if the production organism is not inactivated and/or removed. You should also address

methods used to ensure the integrity of the production organism, such as how you guard against contamination and genetic change. FDA is particularly concerned about contamination when fermentation occurs outside of a sterile production vessel (e.g., production of algae in ponds). Note that the use of a major food allergen in the fermentation medium may require a separate notification or petition to the FDA, unless the presence of the allergen is declared on the product label. See section 403(w) of the FD&C Act (21 U.S.C. 343(w)). If your ingredient is an enzyme, the specifications portion of the identity section of your notification should describe the analytical method used to determine enzyme activity, the specifications for enzyme activity in the NDI, and the acceptance criteria for enzyme activity and for the number of units of activity per serving of the NDI in the dietary supplement. Post-fermentation harvest and processing should be described, including filtration, washing, and preservation methods.

17. **What information should I submit to demonstrate the identity of a live microbial dietary ingredient?**

You should include a complete description of the organism, including:

- the strain,
- methods used to establish the identity of the strain, such as identification by internationally recognized third-party repositories (e.g., the American Type Culture Collection), and
- the relationship of the strain to the strain(s) of the same species used to establish the history of use or other evidence of safety for the dietary ingredient.

The use of scientific names is required for botanical ingredients (21 CFR 190.6(b)(2)) and is recommended for bacteria. For bacteria, FDA recommends using the Bacteriological Code (1990 Revision),[22] validated lists of names in the International Journal of Systematic and Evolutionary Microbiology, and published lists of prokaryotic names with standing in nomenclature (e.g., the German Collection of Microorganisms and Cell Cultures[23] or the List of Prokaryotic Names with Standing in Nomenclature[24]). FDA will pay particularly close attention to the proper identification of organisms from genera or species that do not have a long history of food use and to those from genera, like *Bacillus* and *Streptococcus*, which contain both species with long histories of food use and species known to contain human pathogens. FDA regards all members of a species that contains human pathogens as potentially harmful to human health, and therefore inappropriate for use as dietary ingredients, because of the absence of a consensus that there are valid scientific ways to distinguish between pathogenic and non-pathogenic members of a single species or to prevent horizontal transfer of genes for pathogenic traits between members of the same bacterial species. Examples of species that should not be used as dietary ingredients include *Escherichia coli*, *Enterococcus faecalis*, and *Enterococcus faecium*.

FDA considers each strain of a bacterial or yeast species to be a separate ingredient. You should explain how your strain was obtained and how it varies from other members of the same species. If your strain was genetically modified using either random mutagenesis or bioengineering, you should describe the process used and how you characterized the properties of the new strain.

FDA also considers the manufacturing process, including the fermentation, as an intrinsic part of the identity of an ingredient that is viable at the time of ingestion. The agency recommends that the fermentation and other parts of the manufacturing process be described in detail in your notification, as recommended in question VI.A.16, above.

FDA will pay particular attention to the viability of microorganisms in the NDI. The per-serving level of a viable microorganism depends on both the mass (in grams) and the viability (e.g., number of colony-forming units (CFU)) of the organism in the final product. The composition of the growth medium and the fermentation conditions of the organism are also relevant to the safety of the product, particularly when they alter the form of the organism (e.g., spore versus vegetative) or the composition of the ingredient (e.g., when the ingredient includes both the organism and the growth medium). The notification should explain the relevance of safety information presented about other strains from the same species.

18. **What information should I provide if my notification includes an expiration date or "use by" date for the labeling of the NDI or the dietary supplement to which the NDI will be added?**

The expiration or "use by" date should be based on appropriate supporting stability data showing that (1) no new degradants will form during the labeled shelf life of the product under the conditions of storage specified in the notification, if any, or under normal storage conditions; and (2) the NDI or dietary supplement will continue to meet the critical safety attributes of identity, strength, and purity through its labeled expiration or "use by" date. You should provide these supporting data in the notification.

19. **What information should I submit to describe the conditions of use that I intend to recommend or suggest in the labeling of my dietary supplement?**

Your notification must describe the conditions of use that will be recommended or suggested in the labeling of your dietary supplement or, if no conditions of use will be recommended or suggested in the supplement labeling, the ordinary conditions of use of the supplement (21 CFR 190.6 (b)(2)(ii)). Conditions of use include the dose (serving size), frequency of use (e.g., number of servings per day), duration of use, instructions for use, target population, and any restrictions on use, such as excluded populations.

For purposes of review, daily lifetime use by all age groups at the highest recommended serving size will be assumed. Population restrictions could include exclusion of children, pregnant or lactating women, or sensitive individuals who should not consume the product. Allergen warnings are an example of a population restriction on conditions of use. The conditions of use should be described prominently in the administrative section near the beginning of the notification (see question V.A.2).

B. **History of Use or Other Evidence of Safety**

1. **What safety information is required to support a NDI notification?**

You must provide the information that forms the basis on which you have concluded that a dietary supplement containing the NDI will reasonably be expected to be safe under the supplement's labeled conditions of use (21 U.S.C. 350b(a)(2)). In general, this information should include an adequate history of safe use, safety studies, or both.

2. **Should I submit both a history of safe use and safety testing data for the NDI?**

It depends. A notification should provide evidence of a history of safe use; other evidence of safety, including clinical and/or animal testing; or some combination of history of use and other evidence of safety. The submitted data should provide the basis for a conclusion that there is a reasonable expectation of safety under the proposed conditions of use of the dietary supplement containing

the NDI. FDA expects that when history of use evidence alone is adequate to support the safety of the NDI in the supplement, notifiers will prefer to use that route. Compared to the cost and time needed to conduct clinical or animal toxicology studies, it is generally less expensive and faster to gather historical information and to conduct chemistry studies to establish the identity of the historically used materials. Submitting clinical and/or animal studies in addition to history of use data would be appropriate when the history of use evidence contains gaps or when the proposed conditions of use for the NDI differ from the historical conditions of use.

3. **What data and information should I submit to substantiate a NDI's history of safe use?**

A history of safe use can be substantiated by providing evidence that the substance was safely consumed as a food or dietary supplement or as a component of a more complex mixture (e.g., calcium in milk or beta-glucan in oatmeal) at levels equal to or higher than those that would be consumed by someone taking the NDI-containing supplement under the proposed conditions of use.

Elements that FDA recommends to substantiate that a NDI has a history of safe use include (1) a characterization and comparison of the identity of the NDI and the historically consumed article, and (2) an explanation of how the compositions of the two are related. That is, the composition and identity of the NDI and the historically consumed article should be characterized in sufficient detail to demonstrate that safe use of the historically consumed article is relevant to the safety of the NDI and provides a basis to conclude that the supplement in which the NDI will be marketed will reasonably be expected to be safe under the proposed conditions of use. If the NDI's history of use was as a component of a more complex mixture, you should demonstrate how the NDI is qualitatively and quantitatively related to the historically consumed component. If the NDI is itself a mixture of dietary ingredients, you should demonstrate how the component dietary ingredients in the NDI are related to historically consumed ingredients or components.

In addition, (a) the dose (amount per serving) and total daily intake, (b) duration of use, (c) frequency of intake, and (d)any additional information that describes the conditions of use of the historically consumed material should be provided.For example, if consumption is not uniform within the population, you should provide information about the mean and high (e.g., 90th percentile) exposure levels. Finally, the size and relevant characteristics of the consuming population (e.g., everyone vs. limitations based on age, gender, or health status) should be discussed.

For these data to be useful, the intake level for the historically consumed article should be the same as or higher than the anticipated intake level of the NDI in the dietary supplement, based on the conditions of use described in the NDI notification.

For example, information showing that a steroid hormone is present in nanogram amounts in a serving of milk or beef -- foods that have a long history of safe use -- would not support the safety of a highly concentrated bovine extract that contains the steroid hormone in milligram amounts.

In contrast, consumption of cow's milk could be used to support the safety of a specific protein purified from milk at a serving level equal to or lower than the amount of the protein found in an 8 ounce serving of milk.

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 expected to be safe based on compositional information alone.

The safety assessment should describe and discuss situations in which the conditions of use and composition of the NDI differ from the documented conditions of use and composition of the historically consumed substance (e.g., when the NDI is derived from a plant variety bred to produce an additional constituent or to remove a toxic constituent). When the historical usage differs substantially from the proposed use of the NDI, additional supportive data may be needed. Examples of differences in a NDI's proposed use that might necessitate further supportive data include: higher dosage, different route of administration (e.g., an article that has been consumed in sublingual form and is now intended for ingestion as a NDI), longer duration of use, other changes that increase exposure to potential toxic effects, and any other difference that raises new safety issues, such as a change in target population (see definition in section VII).

4. **What documentation of a NDI's history of use should I submit?**

Documentation of a NDI's history of safe use in food could include published data and information, such as peer-reviewed scientific literature, reports from authoritative bodies, survey data on food or nutrient composition and consumption, advertisements or other published promotional material describing the composition of products, published agricultural or food production data, or cookbooks or other published recipes documenting the use of an ingredient to prepare conventional foods. Documentation of history of use could also include trade secret or confidential commercial information, such as proprietary survey or consumption data, product sales data, and compositional analyses.

5. **Am I required to submit a comprehensive survey of every historical use of the NDI?**

No, only the data and information on which your reasonable expectation of safety is based are required. For example, if you have documentation that soybeans have a history of safe use in a large population in Asia, data describing lower historical consumption in the U.S. or Europe is not necessary to address the safety of a NDI that is a constituent of soybeans.

6. **How do I determine whether historical use was "daily" or "intermittent," and what do the terms "chronic" and "sub-chronic" mean?**

Daily use of the historically consumed material refers to ingestion at least once a day, every day, for at least three months in a row or for more than 90 days in a year. Intermittent use is any use that is less frequent than daily use. FDA assumes that conditions of use that specify daily use are referring to daily lifetime use, unless a shorter duration of use is specified in the notification. Chronic use means long-term use, which FDA assumes to be consumption of the substance every day by men, women and children throughout life, unless the notification specifies otherwise. This is in contrast to sub-chronic use, which is by definition intermittent. Intermittent use can be either daily and finite in duration or non-daily and lifetime in duration. For example, a rodent study in which a dietary supplement is fed daily for 90 days is a sub-chronic study (see also question VI.B.30).

7. **Should I estimate the intake of historically consumed materials related to my NDI if I am relying on those related materials to establish a history of safe use, and should this estimate be included in my NDI notification?**

Yes to both questions. If your conclusion that the dietary supplement containing your NDI will reasonably be expected to be safe is based on a history of safe use of materials other than the NDI itself, you should estimate the historical intake of the materials that you determine to be relevant (see question VI.A.9) and include this information in your NDI notification. In developing these estimates, you should take into account the complete pattern of intake, including dose, duration, and frequency of intake, as well as the size of the population known to have consumed the substance. The distribution of intake within the population (e.g., the amount consumed by the

mean or by the 90% of the population with the highest intake) is also important.

8. **Where may I find information on how to estimate consumer intake?**

For references and information on methods of estimating consumer intake of food ingredients, including dietary ingredients in dietary supplements, refer to "Estimating Dietary Intake of Substances in Food"[25] and section III.G, "Intake Estimate," in "Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions."[26] FDA is also aware of the existence of extensive analyses of consumption of specific conventional foods, especially in the U.S., in proprietary databases. Because these proprietary databases contain food categories much narrower than those described in public databases, they may be helpful in estimating consumer intake of a food constituent that becomes a NDI for use in a dietary supplement.

9. **How is the reliability of the history of use data evaluated?**

An important component of reliability is the length of an ingredient's history of use. A description of the population and the ways in which they use the food is also important. The frequency of food consumption and the number of consumers who used the food are at least as important as the number of years over which the product was available. Because there is little scientific literature addressing this topic, FDA cannot make specific recommendations at this time, although the agency considers 25 years of widespread use to be the minimum to establish a history of safe use.[27]

10. **Should I cite the history of use of a NDI in traditional medicine?**

It depends on how much information is available about the use of the NDI in traditional medicine and how similar the traditional medicine use is to the proposed use in a dietary supplement. The history of use of a NDI in traditional medicine can help to establish a reasonable expectation of safety for the NDI's use in a dietary supplement. However, because differences in composition, conditions of use, and target population often limit the relevance of a safe history of use in traditional medicine to the safety of a NDI in a dietary supplement, additional safety information is almost always needed. As previously described, it is important to document the size and characteristics of the population that consumed the NDI in or as a traditional medicine, as well as conditions of use such as dose, duration and frequency (see VI.B.3 and VI.B.7). In addition, if the medicinal product was consumed under the supervision of a trained practitioner of traditional medicine, it is important to document safety-related restrictions on use within the written or oral tradition. Often, traditional medicinal products are chemically and compositionally very different from the NDI that is the subject of the NDI notification. Therefore, it is important to document and explain how any information about a substance's history of safe use in traditional medicine is qualitatively and quantitatively related to the NDI that is the subject of the notification and its proposed conditions of use.

11. **Are additional animal and human studies needed to support evidence of a history of safe use by humans?**

It depends on the situation. Data on history of use in humans should be the first evidence considered in evaluating the safety of a NDI. When the NDI has been previously consumed by humans, additional animal or human safety data are seldom needed if (1) the proposed use level is similar to or less than the levels safely consumed by humans in the past, and (2) the population expected to consume the NDI is the same as, or a subset of, the population that safely consumed the substance in the past. In many cases, no additional animal or human safety data are needed because the NDI is reasonably expected to be safe based on a large margin of safety between the level shown to cause no observed adverse effects in humans and the intake level that would result from the proposed use of the NDI in the dietary supplement, or based on longstanding and widespread use of the ingredient as a constituent of conventional food at or below the intake level that would result from the proposed use of the NDI in the dietary supplement.

When the historical use differs significantly from the proposed use of the NDI in a dietary supplement, however, additional supportive data are usually needed. Examples of differences in proposed use that would ordinarily necessitate further supportive data include: higher dosage than the historical use, different route of administration, longer duration of administration, other changes that increase exposure to potential toxic effects, and any other differences which raise new safety concerns (e.g., a different target population). These examples are based on the general principle that the risk of a substance is likely to increase as intake increases above levels safely consumed in the past. When historical use of a NDI differs significantly from the proposed dietary supplement use, FDA encourages you to submit additional animal studies, human studies, or both. Such studies should be designed to address gaps in the history of use evidence.

12. **What other factors would be helpful in determining when animal or human safety studies are needed in addition to history of use data?**

Generally, the best way to determine whether history of use data provide a basis for a reasonable expectation that a dietary supplement containing a NDI will be safe is to compare the conditions of use proposed in the NDI notification with the documented historical conditions of safe use. The following are examples of situations where FDA would typically recommend that history of use data be supplemented with additional animal or human safety studies:

- Higher proposed serving level or total daily intake level
- Longer proposed duration of consumption than historically reported (e.g., notification states that NDI will be marketed with labeling that recommends or implies continuous daily use for improved digestive function, but the history of safe use involves only infrequent, short-term use for indigestion)
- Different proposed route of administration (e.g., data about historical use of a substance as a poultice or by injection ordinarily would not be sufficient to support the safety of a NDI for use in a dietary supplement, which by definition is intended for ingestion)
- A change from historical use that might increase potential toxic effects (e.g., the NDI will be sold as capsules of a ground leaf, but the form historically used was a tea made from the plant's roots)
- A change in the target population (e.g., history of safe use has been established in adults, but NDI will be used in a dietary supplement marketed for use by young children)

13. **Can I use toxicology or clinical studies published by others, or unpublished studies I have performed, if those studies used test articles that are similar but not identical to the NDI or the supplement containing the NDI?**

FDA generally recommends that the substance used in safety studies be identical to the NDI or the dietary supplement that is the subject of your notification. However, in the absence of safety data on the NDI or supplement itself, it may be useful to provide data on the safety of a related substance or product. For example, if the NDI is a component of another substance for which safety studies are

available, it may be helpful to submit data from those studies, accompanied by an explanation of why the data on the related substance support the safety of your NDI. Data from a study involving the oral administration of the dried ground root of a plant could be relevant to the safety of a NDI that is an isopropanol extract of the same root if you document that the components of the isopropanol extract were present at the same or lower levels in the ground root fed to the study subjects. The safety of an ester ingredient can be inferred if you can provide data to demonstrate that the ingredient is rapidly hydrolyzed in the stomach or intestine into an acid and an alcohol, and that the acid and the alcohol each have a long history of safe use in food. The more different the composition of the test article in a study is from that of the NDI, however, the more difficult it will be to argue that the study is relevant.

14. **Are there scenarios in which additional safety data would not be needed if the proposed use of the NDI leads to intake levels that are the same as or less than the levels consumed historically?**

    Yes. When the proposed use of the NDI leads to intake levels that are the same as or less than the levels for which there is a documented history of safe use, additional safety data are not needed if the dietary supplement containing the NDI is intended for (1) daily chronic use, and the documented historical use data support safe daily chronic use in the same population or a broader population; (2) intermittent use, and the documented historical use data support safe intermittent use in the same population or a broader population; or (3) intermittent use, and the documented historical use data support safe daily chronic use in the same population or a broader population. (See Table 2: Safety Testing Recommendations Matrix.)

15. **What types of data would help in assessing safety if the dietary supplement containing the NDI is intended for daily chronic use, the NDI has a documented history of safe intermittent use, and the proposed use of the NDI leads to intake levels that are the same as or less than the levels consumed historically?**

    1. (1) A three-study genetic toxicity (genetox) battery (bacterial mutagenesis, *in vitro* cytogenetics, and *in vivo* mammalian test) that includes a test for gene mutations in bacteria, either an *in vitro* mouse lymphoma thymidine kinase+/- gene mutation assay (preferred) or another suitable *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells, and an *in vivo* test for chromosomal damage using mammalian hematopoietic cells;
    2. (2) a 14-day range-finding oral study to establish a maximum tolerated dose (MTD) in an appropriate animal model;
    3. (3) a 90-day sub-chronic oral study (see questions VI.B.6, VI.B.29-31)in the same species as the range-finding study to establish an MTD and a No Observed Adverse Effect Level (NOAEL) for use in calculating the margin of safety;
    4. (4) a multi-generation rodent reproductive study (minimum of two generations); and
    5. (5) a teratology study (rodent or non-rodent);

    except that the latter two studies are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger. (See Table 2: Safety Testing Recommendations Matrix.)

16. **What types of data would help in assessing safety if the dietary supplement containing the NDI is intended for daily chronic use, the NDI has a documented history of safe daily chronic use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?**

    1. (1) A two-study genetox battery (bacterial mutagenesis and *in vitro* cytogenetics) that includes a test for gene mutations in bacteria, either an *in vitro* mouse lymphoma thymidine kinase+/- gene mutation assay (preferred) or another suitable *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells;
    2. (2) a 14-day range-finding oral study to establish an MTD in an appropriate animal model;
    3. (3) a 90-day sub-chronic oral study (same species as the range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety;
    4. (4) a repeat-dose tolerability study in humans (30-90 day duration); (5) a one-year chronic toxicity study in an appropriate animal model or a two-year carcinogenesis study in rodents;
    5. (6) a one-generation rodent reproductive study; and
    6. (7) a teratology study (rodent or non-rodent);

    except that the latter two studies are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger. (See Table 2: Safety Testing Recommendations Matrix.)

17. **What types of data would help in assessing safety if the dietary supplement containing the NDI is intended for daily chronic use, the NDI has a documented history of safe intermittent use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?**

    1. (1) A three-study genetox battery as described in question 15;
    2. (2) 14-day range-finding oral studies to establish a maximum tolerated dose (MTD) in at least two appropriate species, at least one of which is non-rodent;
    3. (3) two 90-day sub-chronic oral studies (one for each species for which there is a range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety;
    4. (4) a one-year chronic toxicity study in an appropriate animal model or a two-year carcinogenesis study in rodents;
    5. (5) a repeat-dose tolerability study in humans (30-90 day duration);
    6. (6) a multi-generation rodent reproductive study (minimum of two generations); and
    7. (7) a teratology study (rodent or non-rodent);

    except that the latter two studies are generally not needed if the product is labeled as not for use by women of childbearing

age, pregnant or lactating women, and children 13 and younger. (See Table 2: Safety Testing Recommendations Matrix.)

18. **What types of data would help in assessing safety if the dietary supplement containing the NDI is intended for intermittent use, the NDI has a documented history of safe intermittent use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?**

    1. (1) A two-study genetox battery (bacterial mutagenesis and *in vitro* cytogenetics) as described in question 16;
    2. (2) a 14-day range-finding oral study to establish a maximum tolerated dose (MTD) in an appropriate animal model;
    3. (3) a 90-day sub-chronic oral study (same species as the range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety;
    4. (4) a single-dose or repeat-dose tolerability study in humans and/or an ADME study in animals and/or humans;
    5. (5) a one-generation rodent reproductive study; and
    6. (6) a teratology study (rodent or non-rodent);

    except that the latter two studies are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger. (See Table 2: Safety Testing Recommendations Matrix.)

19. **What types of data would help in assessing safety if the dietary supplement containing the NDI is intended for intermittent use, the NDI has a documented history of safe daily chronic use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?**

    1. (1) A two-study genetox battery as described in question 16;
    2. (2) a 14-day range-finding oral study to establish a maximum tolerated dose (MTD) in an appropriate animal model;
    3. (3) a 90-day sub-chronic oral study (same species as the range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety;
    4. (4) a single-dose or repeat-dose tolerability study in humans and/or an ADME study in animals and/or humans; and
    5. (5) a teratology study (rodent or non-rodent);

    except that the teratology study is not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger. (See Table 2: Safety Testing Recommendations Matrix.)

20. **What types of data would help in assessing safety if there is no history of use of the NDI that can be relied on to provide evidence of safe use in dietary supplements?**

    1. (1) A three-study genetox battery as described in question 15;
    2. (2) 14-day range-finding oral studies to establish a maximum tolerated dose (MTD) in at least two appropriate species, at least one of which is non-rodent;
    3. (3) two 90-day sub-chronic oral studies (one for each species for which there is a range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety (see footnote "‡" in Table 2: Safety Testing Recommendations Matrix);
    4. (4) a repeat-dose tolerability study in humans and/or an ADME study in animals and/or humans (30-90 day duration);
    5. (5) if proposed use is either intermittent or daily chronic, a one-year chronic toxicity study or a two-year carcinogenesis study in at least two animal species;
    6. (6) a multi-generation rodent reproductive study (minimum of two generations); and
    7. (7) a teratology study (rodent or non-rodent);

    except that the latter two studies are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger.

    Note: Based on the nature of the NDI and the results of other testing, special studies (e.g., carcinogenicity, ADME) may be needed to provide a reasonable expectation of safety. Other nonclinical studies to assess immunotoxicity and neurotoxicity should be conducted on a case-by-case basis, as appropriate. (See Table 2: Safety Testing Recommendations Matrix.)

TABLE 2: Safety Testing Recommendations Matrix

Documented Historical Use	Proposed Use of the NDI		Two-Study Genetic Toxicity Battery §	Three-Study Genetic Toxicity Battery§	14-Day Range-Finding Oral Study in Animals	90-Day Sub-chronic Oral Study in Animals†	One-Generation Rodent Reproductive Study	Multi-Generation Rodent Reproductive Study	Teratology Study in Animals	One-Year Chronic Toxicity or Two-Year Carcinogenesis Study in Animals*	Single-Dose Tolerability and/or ADME Study in Animals and/or Humans*	Repeat-Dose Tolerability and/or ADME Study in Animals and/or Humans*
	Intermittent	Less Than Historical Use (see Question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									

Daily Chronic		Greater Than Historical Use (see Question VI.B.19)	✓		✓	✓			✓		✓	
	Daily Chronic	Less Than Historical Use (see Question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
		Greater Than Historical Use (see Question VI.B.16)	✓		✓	✓	✓		✓	✓		✓
Intermittent	Intermittent	Less Than Historical Use (see Question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
		Greater Than Historical Use (see Question VI.B.18)	✓		✓	✓	✓		✓		✓	
	Daily Chronic	Less Than Historical Use (see Question VI.B.15)		✓	✓	✓		✓	✓			
		Greater Than Historical Use (see Question VI.B.17)		✓	✓	✓‡		✓	✓	✓‡		✓
No History	Daily Chronic (see Question VI.B.20)			✓	✓	✓‡		✓	✓	✓‡		✓
	Intermittent (see Question VI.B.20)			✓	✓	✓‡		✓	✓	✓‡		✓

§ Genetic toxicity batteries are described in Questions 15 and 16.

† Reproductive and teratology testing is not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger.

‡ In general, if there is no history of use, two species should be used for 90-day sub-chronic studies. In addition, the one-year chronic toxicity study or two-year carcinogenesis study should be done in two species. However, the one-year chronic toxicity study, two-year carcinogenesis study, or second sub-chronic study may not be necessary in some cases based on the amount and type of historical use data or the duration of use of the NDI, if significantly shorter than lifetime daily use. For example, if the proposed use of the NDI is for 30 days or less, then a 28-day animal study might be sufficient under certain circumstances (e.g., live microbial NDI).

* Special studies such as one-year chronic toxicity studies in animals, two-year carcinogenicity studies in animals, and ADME, bioavailability, and tolerability studies in animals and/or humans should be conducted on a case-by-case basis, as appropriate, if the toxicology data or the identity of the NDI raise a special safety concern.

21. **Where can I find FDA's current thinking about testing for food and color additives, and can I rely on this information when preparing my NDI notification?**

FDA's current thinking about testing for food and color additives is discussed in "Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000)."[28] This document provides general guidance on conducting standard toxicity tests. It also includes guidelines on conducting certain genetic toxicity tests, short-term toxicity tests, sub-chronic toxicity tests, one-year toxicity studies, and reproductive and developmental toxicity studies.

You should use your own best judgment in compiling scientific evidence that provides a basis to conclude that the NDI that is the subject of your notification will reasonably be expected to be safe when used under the conditions recommended or suggested in the labeling of the dietary supplement described in the notification. The NDI safety standard is different than the standard for food additives, drugs, pesticides, and other FDA-regulated products. Recommendations in guidance documents that are tailored to the safety assessment needs of other FDA-regulated products may not always be appropriate for dietary ingredients and dietary supplements.

22. **Am I required to use only FDA-published safety test protocols?**

No. Because there are no safety test protocols developed specifically for dietary ingredients, you should use your own judgment in selecting among FDA's protocols and other internationally recognized safety testing protocols and testing batteries developed for other types of products when you choose safety testing protocols for your NDI or the dietary supplement to which your NDI will be added. Regardless of the protocols used, you should cite the source for each protocol and why the protocol or the battery of protocols you chose is appropriate for the safety endpoints that are being investigated.

23. **What are some sources of safety testing protocols that can be used in testing NDIs?**

Useful guidelines for safety testing include:

- FDA's "Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000)"[29];
- OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects, published by the Organisation for Economic Co-operation and Development[30];
- "Harmonized Test Guidelines," published by the Office of Chemical Safety and Pollution Prevention of the U.S. Environmental Protection Agency (EPA)[31]; and
- "Safety Guidelines," published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[32]

24. **What is the appropriate highest dose of a NDI to use in animal and human safety studies?**

To maximize the chance that toxicity associated with the test article can be detected, the highest dose (commonly referred to as the "top dose") in animal studies should be the maximum tolerated dose (MTD) (see definition in Section VII). Lower doses are used to establish the dose-response relationship and the no-effect dose (see question VI.C.4 concerning discussion of NOAEL). Shorter-term studies are needed to estimate the MTD for longer studies; for example, the results of a 14-day study must be known before the dose for a 90-day study can be determined. Considering a broad range of biological information is essential to pick the correct top dose or MTD. For example, data concerning changes in body and organ weight and clinically significant alterations in hematological, urinary, neurological, and clinical chemistry parameters, in combination with more definitive toxic, gross, or histopathologic endpoints, can be used to estimate the MTD. FDA intends to consider whether the test article was tested at the MTD as a major factor in evaluating the adequacy of studies submitted in a NDI notification. The studies should include a description of the process used to select the MTD for the study, if it is not readily apparent.

Please note that it is not scientifically valid to select doses for tests based on information unrelated to the toxicity of the test article. For example, the highest dose should not be selected so as to provide a pre-determined margin of safety over the maximum expected human consumption of the test article, assuming that the results of testing at that dose will be negative. FDA recognizes that there may be limitations on using a top dose. For example, limits on top doses can be based on animal handling considerations, such as the amount that can be safely administered by gavage or the amount in feed that still permits proper nutrition. The top dose in clinical studies should be governed by safety considerations, as determined by an Institutional Review Board (IRB). However, in clinical trials, the top dose should be as high as feasible. At a minimum, the top dose or total daily intake level in a clinical trial of a NDI should be as high as the top dose or total daily intake level of the NDI under the conditions of use proposed in the notification. Preferably, the top total daily intake level in the trial should be higher than the proposed top total daily intake level of the NDI.

25. **What should I do to justify the use of a particular protocol?**

You should cite an authoritative source for the protocol and explain how information generated by the study using the protocol supports the safety of the dietary supplement in which the NDI will be used. If you decide to deviate from a standard or published protocol, you should explain why you altered the protocol and how the alteration affects the relevance of the study results to the safety of your product.

26. **How will I identify a potential hazard using a standard genetic toxicity test, and what should I do after identifying a potential genetic toxicity hazard?**

A positive finding in one or more of the standard genetic toxicity tests constitutes a clear but non-quantitative identification of a potential hazard. Positive results in genetic toxicity tests may necessitate additional safety testing, such as an evaluation of carcinogenicity from two-year or lifetime chronic toxicity assays. General guidance on following up positive results in genetic toxicity testing can be found in the scientific literature on this topic.[33]

27. **Should the NDI notification discuss the history of use or other evidence of safety that forms the basis for my conclusion that a genotoxic dietary ingredient can reasonably be expected to be safe?**

Yes. This history of use or other evidence of safety should be addressed in your NDI notification. A risk assessment should be used to determine whether the genetic toxicity of the NDI prevents the dietary supplement from being reasonably expected to be safe under the intended conditions of use.

28. **Where can I find good examples of genotoxicity protocols that can be used in conducting animal and human studies on new dietary ingredients?**

The sources cited in the answers to questions VI.B.21 and VI.B.23 contain test guidelines and testing batteries for evaluating genetic toxicity. The Redbook 2000[34] is particularly relevant to safety testing of food ingredients.

29. **What is the purpose of a sub-chronic oral toxicity study?**

When properly conducted (e.g., with doses selected based on shorter term repeat-dose studies), sub-chronic oral toxicity studies are used to identify the maximum tolerated dose (MTD) of a substance, as well as the substance's No Observed Adverse Effect Level (NOAEL). Toxicity data and the NOAEL identified by the sub-chronic oral study are used 1) to predict the organ toxicity or other types of toxicity that are likely to be associated with human or animal consumption of unsafe quantities of the test article, 2) to determine the need for and design of additional animal studies, such as specialized toxicity studies and chronic toxicity studies, and 3) to assess the safety of short-term repeat-dose exposure to the test article, either for consumers or for participants in clinical trials.

30. **What is the appropriate duration for a sub-chronic oral toxicity study?**

Sub-chronic oral toxicity studies are generally conducted for at least 90 days (3 months). Protocols described as lasting 12 or 13 weeks are considered equivalent. The 90-day study provides information on the possible health hazards likely to arise from repeated exposure to a substance over a three-month period of time.

31. **Where can I find more information and examples of a sub-chronic oral study?**

For further information and sample protocols, we recommend that you refer to the Redbook 2000 on FDA's website,[35] which includes guidelines for sub-chronic oral toxicity studies with rodents and sub-chronic oral toxicity studies with non-rodents. OECD Guidelines for the Testing of Chemicals, Guideline 408 ("Repeated Dose 90-day Oral Toxicity Study in Rodents:)[36] also provides protocols for rodent studies. The appropriate animal species and study design may vary depending on the safety questions associated with the NDI being studied.

32. **What is the purpose of reproductive toxicity and teratology studies?**

The purpose of reproductive toxicity studies is to provide information regarding the effects of a dietary ingredient on all aspects of reproduction, including sexual behavior, spermatogenic and estrus cycles, gonadal function, fertility, parturition, lactation, and pre-natal development. The purpose of teratology studies is to provide information on whether the test article causes congenital malformations in the offspring of a test animal. The purpose of multi-generation reproductive studies is to provide growth and reproductive function data regarding the effects of the test article on male and female offspring of test animals and on the growth and reproductive function of their offspring in the subsequent generation(s).

33. **Should I include a discussion of the reproductive and teratology studies in my NDI notification?**

Yes. FDA recommends that you provide a summary and a detailed discussion of the results of each reproductive and teratology study in the Comprehensive Safety Profile for the NDI (see VI.C.2, below).

34. **Should I identify the "No Observed Adverse Effect Level" (NOAEL) for all test substance-related changes in both reproductive and teratology test endpoints?**

Yes. You should identify the NOAEL for parental animals and their offspring in each generation in reproductive studies, including teratology studies. In addition to information about reproductive success, data from the study should also be used to provide information on development (i.e., growth and function of the offspring) and teratogenesis (i.e., birth defects, both structural and functional).

35. **Where can I find sample protocols for reproductive and teratology studies?**

We recommend that you refer to the OECD Guidelines for the Testing of Chemicals, Guidelines 415 (One-Generation Reproduction Toxicity Study),[37] 416 (Two-Generation Reproduction Toxicity),[38] 421 (Reproduction/Developmental Toxicity Screening Test),[39] and 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test)[40] to find protocols for conducting reproductive toxicity and teratology studies. You may also refer to the guidelines for reproductive studies in section IV.C.9 of the Redbook 2000, "Guidelines for Reproduction Studies,"[41] for guidance on conducting reproduction and developmental toxicity studies, including reproduction testing with a teratology phase. Information about how data from these studies are assembled and used for other regulatory programs [e.g., pesticides (see EPA's "Harmonized Test Guidelines")[42] and medicinal products (see ICH's "Safety Guidelines")][43] may also be helpful. In particular, "Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility"[44] contains useful guidelines for detecting reproductive toxicity.

36. **What is the purpose of repeat-dose toxicity testing?**

In general, the purpose of repeat-dose toxicity testing is to define toxic effects on body systems and target organs based on repeated and/or cumulative exposure to the test substance or to constituents and/or metabolites of the test substance. Repeat-dose testing defines the nature of the tissue or organ damage, particularly in relation to dose and duration of exposure. Repeat-dose testing is also used to identify dosages associated with toxic and biological responses and to define a NOAEL. The route of administration in repeat-dose testing for a dietary supplement containing a NDI should always be oral, and the study should include a range of doses at and above the proposed dose of the NDI in the dietary supplement. An "oral study," as described in this guidance, can include administration in feed or drinking water (with the feed or water consumption measured to confirm actual intake) or via gavage, which involves introduction of the test article through a tube passed through the mouth into the stomach. The test article used in these studies should have the same composition (including excipients) and form as the dietary supplement described in the notification.

37. **Am I required to conduct human clinical studies to support the safety of my NDI or the dietary supplement containing my NDI?**

The FD&C Act contains no explicit requirement for a manufacturer or distributor to conduct human clinical studies before submitting a NDI notification. However, there may be circumstances in which you find it necessary to perform such studies because the existing history of use data, safety data, and data on population exposure do not provide a sufficient basis for you to conclude that the dietary supplement containing the NDI will reasonably be expected to be safe under its proposed conditions of use.

38. **What kinds of human clinical studies are useful to support the safety of a NDI?**

The most useful studies are usually short-term tolerability studies and ADME studies. When human ADME studies are done in conjunction with ADME studies conducted in the animal species used for toxicological testing, the relevance of the animal data to humans can be demonstrated and the safety factors used to calculate the margin of safety can be reduced (see VI.C.5).

Tolerability studies identify acute toxicity, such as that associated with toxins or indigestible nutrients, at very high serving levels of ingredients like fats and oils.Human repeat-dose studies are more rarely used to directly demonstrate the safety of the test article in humans. They can be used to allay specific safety concerns raised by animal studies or history of use information, or to establish a margin of safety for a NDI when the proposed conditions of use would result in doses that cannot be humanely administered to animals.

39. **What is the purpose of "repeat-dose" human studies, and how are such studies classified?**

If animal toxicity studies or history of use data do not document an adequate margin of safety between the NOAEL for your NDI and the expected intake of the NDI from its proposed dietary supplement use, we recommend a human clinical trial consisting of a repeat-dose study. Clinical trials should include both males and females, as well as an adequate sample size and duration. Sample size is a very important consideration, as the study should be sufficiently powered to show differences in your data. If a clinical trial is not powered by a large enough sample size, results showing no adverse effects cannot be relied on as evidence of safety because the absence of adverse effects from intake of the NDI could be due to chance. Duration of the clinical trial is also an important factor in your study design because it should be long enough to mimic chronic consumption. The clinical trial should last at least 90 days, and its endpoints should be clearly defined.

Clinical trials may be grouped by their purpose and objective. Phase I trials are the first stage of testing in humans. They are designed to assess absorption, distribution, metabolism, and excretion (ADME), safety, tolerability, pharmacokinetics, and pharmacodynamics. Phase I studies are generally single-dose studies, followed by dose-range or dose escalation studies, and finally short-term repeat-dose studies to evaluate pharmacokinetic parameters and tolerance (see Table 2: **Safety Testing Recommendations Matrix**). Single-dose and repeat-dose studies are elements of Phase I studies to assess human pharmacology. Phase II studies (designed to assess dosing requirements and efficacy) and Phase III studies (randomized, controlled multicenter studies involving large sample sizes to evaluate effectiveness of a treatment) focus on efficacy and are generally not useful to establish the safety of a dietary supplement.

40. **Where can I find more information and examples of clinical protocols that can be used in conducting human studies for NDIs and dietary supplements?**

For more information and sample clinical protocols, refer to Chapters V[45] and VI[46] of the Draft Redbook II, which provide general guidance on conducting human clinical studies on foods and food ingredients. FDA also recommends consulting "Guidance for Industry--M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"[47] for its discussion of selecting an appropriate dose for sub-chronic oral studies in animals and clinical trials in human volunteers (pp. 1-5).

41. **What information should I submit to demonstrate the safety of a NDI produced by fermentation using microorganisms like bacteria or yeast?**

You should identify the microorganism using scientifically valid nomenclature for the genus, species, and the name of the strain. You should also discuss the history of use of the organism or related organisms as food or to produce food. In addition, you should identify any human pathogens that are phylogenetically related to the fermentation microorganism at the species or genus level. You should also identify any toxins, classes of toxins, or other deleterious substances known to be present in the same species as the microorganism or in a genus or species that is phylogenetically related to the microorganism. Finally, you should document the absence (or the amount, if present) of such toxins or other deleterious substances in the microorganism. The absence of unsafe levels of such deleterious substances should be demonstrated by an appropriate combination of specifications for the NDI, safety testing in humans, and/or safety testing in an appropriate animal model.

42. **What information should I submit to demonstrate the safety of a microbial NDI (live or killed)?**

You should identify any human pathogens that are phylogenetically related to the microbial NDI at the species or genus level. You should identify any toxins, classes of toxins, or other deleterious substances known to be present in the same species or in a phylogenetically related family or genus. You should also document the absence (or the amount, if present) of such toxins or other deleterious substances in the NDI. You should document resistance to any clinically relevant antibiotics, and if applicable, the genetic nature of the resistance. If the microbial NDI is resistant to any clinically relevant antibiotics, it is also recommended that you perform an assessment of the ability of the antibiotic resistance genes to mobilize and transfer to human pathogens under the conditions of use of the dietary supplement.

If your notification cites the history of use of a live microorganism as evidence of safety, FDA recommends a careful assessment of the relative level of historical exposure compared to the proposed conditions of use of the NDI, including a discussion of how the form of the dietary supplement and any excipients used in it affect delivery of the NDI to various points in the human gastrointestinal tract.

If history of use data are inadequate to support the safety of the microbial NDI, you should include safety studies in humans or appropriate animal models in your notification. FDA considers pigs to be the most appropriate animal model for the human digestive tract. Human or animal safety studies should include measurements of the persistence of the organism in the body after administration, the ability of the organism to translocate outside of the gastrointestinal tract, and tolerance of the ingredient using the proposed serving form. Because this is a rapidly evolving scientific discipline, FDA recommends that notifiers be familiar with the state of the recent scientific literature at the time the

43. **What should I do to demonstrate the safety of a NDI that contains nanomaterials or otherwise involves the application of nanotechnology?**

Because there is little scientific literature discussing the safety of nanomaterials in dietary supplements, FDA recommends that notifiers contact FDA prior to submitting a NDI notification for a NDI that contains nanomaterials or otherwise involves the application of nanotechnology.

C. **Summary of the Basis for Your Conclusion of Safety**

1. **Should my notification include separate safety profiles for the NDI and the dietary supplement in which the NDI will be used?**

Yes. FDA recommends that the discussion of history of use and other evidence of safety in your notification should include two separate safety profiles: first, a comprehensive safety profile evaluating the safety of the NDI, and second, a dietary supplement Safety Narrative explaining why the information in the notification provides a basis to conclude that the dietary supplement that contains the NDI will reasonably be expected to be safe when used under the conditions recommended or suggested in its labeling. Each piece of data or information in the notification should be cited in the Comprehensive Safety Profile, the Safety Narrative, or both, so that it is clear how each piece of data or information is used to form the basis for the safety of the dietary supplement product containing the NDI.

When a notification describes a product containing more than one NDI, FDA recommends including a Comprehensive Safety Profile for each NDI, with the safety of the combination of NDIs addressed in the Safety Narrative. However, when there is history of use or other evidence of safety for the combination of ingredients used in the dietary supplement, it may be appropriate to have a Comprehensive Safety Profile for that combination in addition to a separate profile for each NDI (or instead of separate profiles for individual NDIs when most or all of the safety information is for the combination).

2. **What should I include in my Comprehensive Safety Profile for the NDI?**

The NDI Comprehensive Safety Profile should provide objective summaries of all available human and animal toxicological information (both published and unpublished safety studies) and any other information relevant to the safety assessment of the NDI.

The information in the NDI Comprehensive Safety Profile should substantiate the safe use of the NDI in humans under the proposed

conditions of use described in the notification. A history of use discussion in the NDI Comprehensive Safety Profile should document the identity and historical uses of the NDI, including the amount, frequency, and duration of the historical uses, as well as a description of the size and characteristics of the population that consumed the NDI. To the extent that test articles or materials described in the history of use and other evidence of safety are not identical to the NDI, the similarities and differences should be described, and the applicability of the study to the safety evaluation of the NDI should be explained.

If the NDI notification relies on safety studies, the NDI Comprehensive Safety Profile should qualitatively and quantitatively compare the ingredients tested in each of the studies cited with the NDI. If you cite a study on the feeding of a whole herb to a test animal, and the NDI is an extract of that herb, the NDI Comprehensive Safety Profile should qualitatively and quantitatively compare the dose of the herb to the dose of the NDI. Whenever possible, the notification should identify the effect and no-effect doses in each human and animal study, and the relationships between observed effects and observed adverse effects should be described.

The NDI Comprehensive Safety Profile should identify the NOAEL (see question VI.C.4) and describe the toxicity data or adverse events that were the basis for determining it. The Comprehensive Safety Profile should also describe the Acceptable Daily Intake (ADI) for the NDI and explain how it was calculated (see question VI.C.5). Finally, the Comprehensive Safety Profile should state the basis for the margin of safety for the NDI and how the margin of safety was calculated.

The NDI Comprehensive Safety Profile may need to rely heavily on trade secrets or CCI. Any information in the NDI Comprehensive Safety Profile that you believe to be a trade secret or CCI should be identified as such (see question V.A.16).

3. **What should I include in my dietary supplement Safety Narrative?**

The dietary supplement Safety Narrative should include a concise summary of the scientific basis for your conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe when used under the conditions recommended or suggested in the supplement's labeling. The purpose of the dietary supplement Safety Narrative is to explain how the various pieces of data and information fit together to form the basis for your conclusions about the safety of the dietary supplement.The dietary supplement Safety Narrative should be based on the identity information, safety information, and analyses in other sections of the NDI notification, including the NDI Comprehensive Safety Profile. The dietary supplement Safety Narrative should include a summary of the more detailed discussion in the Comprehensive Safety Profile of how you concluded that the NDI in the dietary supplement will reasonably be expected to be safe based on the margin of safety between the NDI intake level that shows no adverse effects (the NOAEL) and the proposed intake level and conditions of use of the NDI in the dietary supplement.

If the supplement contains dietary ingredients other than the NDI, the dietary supplement Safety Narrative should identify the NOAEL and Acceptable Daily Intake (ADI) for each ingredient (see questions VI.C.4 and VI.C.5), describe the toxicity data or adverse events that were the basis for determining the NOAEL, state the basis for the margin of safety for each ingredient, and discuss whether there is any possible synergy or interaction among any or all ingredients that could affect the safety of the dietary supplement. For each dietary ingredient other than the NDI, the dietary supplement Safety Narrative should concisely evaluate known safety concerns and describe how the notifier concluded that the combination of ingredients can reasonably be expected to be safe. The Safety Narrative should also describe the function of each food additive, color additive and GRAS substance (i.e., each non-dietary ingredient), including the technical effect and the quantity needed to achieve that technical effect. References to the applicable food additive, color additive, or GRAS determination are also recommended.

The dietary supplement Safety Narrative should estimate the human intake of the dietary supplement containing the NDI and describe any potential toxicity or health concerns associated with human consumption of the dietary supplement, particularly if concerns that may result from the proposed use of the dietary supplement by a vulnerable population have been identified. The description of toxicity and health concerns should include the effects of excipients, formulation aids, and other non-dietary ingredients present in the dietary supplement, particularly if they alter the safety profile of one or more ingredients, such as by increasing uptake into the body after ingestion. If any ingredient in the dietary supplement is present at a level close to the ADI, the presence of that ingredient from other sources in the diet should also be addressed. Because of the central importance of the dietary supplement Safety Narrative to the overall conclusion of safety, the dietary supplement Safety Narrative should be written in such a way that it will be comprehensible after FDA has redacted any trade secrets and confidential commercial information and placed the notification in the public docket.

4. **What is the difference between a NOEL and a NOAEL, and which should I use?**

The No-Observed-Adverse-Effect Level (NOAEL) is a number signifying the highest dose or total daily intake level that did not elicit an adverse effect in a properly designed and executed toxicological study.[48] The No-Observable-Effect Level (NOEL) is the highest dose at which no effects are observed, including beneficial and neutral effects as well as adverse effects. Therefore, the NOAEL, which is the threshold for adverse effects, is the appropriate level to use in calculating the margin of safety for a NDI.

FDA expects that many dietary ingredients, because they are intended to have beneficial nutritional effects or other effects on the structure or function of the body, will cause changes in parameters that are measured in animal and clinical safety studies. FDA also expects that, as dose and total intake increase, effects that are neutral or beneficial at lower exposures may become adverse effects or be supplanted by adverse effects. Thus, it is important that the notification contain a discussion of the nature of the effects that are observed in safety studies. This discussion should distinguish between adverse effects and other effects (neutral or beneficial effects). The purpose of the NOAEL, which is typically higher than the NOEL, is to identify a safe level of a substance (that is, the level at which no adverse effects are observed), and therefore the NOAEL should be used to calculate the margin of safety in the NDI notification. A comparative discussion of the effects observed at different doses of a NDI should appear in the comprehensive safety profile for the NDI. FDA also recommends that this discussion be summarized in the dietary supplement Safety Narrative because it is central to the overall safety evaluation.

5. **What safety factors should be used if only animal toxicity studies are available?**

It is important for the notifier to determine the acceptable daily intake (ADI), in addition to the NOAEL, to conduct an adequate risk assessment of the NDI. The NOAEL, expressed on a body weight basis (e.g., mg/kg/day), is divided by a safety factor (also referred to as an uncertainty factor) to derive the ADI. Safety factors account for the uncertainty in extrapolating from experimental data to predict the safety of a substance in humans. If the NOAEL is derived from a chronic toxicity study (one-year duration or longer) in animals, the combined safety factor is usually 100. This number is calculated using a factor of 10 to account for interspecies variation between animals and humans and another factor of 10 to account for the variation in sensitivity within the human population. Extrapolation from sub-chronic toxicity studies to chronic use of a NDI or dietary supplement necessitates an additional safety factor. In this situation, FDA recommends using at least two sub-chronic toxicity studies, at least one of which was conducted in a non-rodent species and the other in a rodent species, and introducing another safety factor of 10 for a combined safety factor of 1000.In the absence of supporting history

of use data; using only a single rodent sub-chronic toxicity study as a basis to conclude that chronic use of a NDI in humans will be safe is strongly discouraged, but may be acceptable if a safety factor of 2000 is used and there is no toxicity to the rodents at the maximum tolerated dose (MTD).The additional safety factor of 2 is used in this situation because a complete animal toxicology assessment includes two sub-chronic (90-day) animal studies. The safety factors in these examples are approximate values, which can vary with the specific data that are available. For example, a higher value may be appropriate if toxicity is particularly severe or the variation in human sensitivity is expected to be great. On the other hand, a lower value may be appropriate if sub-chronic studies in both rodent and non-rodent species showed no adverse effects. If human data from chronic toxicity or ADME studies (typically one year in duration) are available, a safety factor lower than 100 may be appropriate. While FDA does not consider the ADI to be a sharp dividing line between safe and unsafe levels, the ADI does provide a useful benchmark for protecting the consumer.

In summary, safety factors are uncertainty factors used multiplicatively to arrive at the combined safety factor that is applied to a particular dataset provided in a notification. Safety factors are used to calculate the ADI (see VI.C.3).

ADI = NOAEL/combined safety factor = NOAEL/ ($Uf_{intra} \times Uf_{extrap} \times Uf_{inter}$)

- Uf_{intra}: An uncertainty factor to account for *intraspecies* variation is introduced to protect sensitive members of the population when clinical trials include only healthy subjects since food is consumed by everyone: the young, the aged, the healthy and the infirm. A value of 10 is usually used. The size of the intraspecies uncertainty factor should be smaller when there is a long history of food use by a large, diverse population. The size of the intraspecies uncertainty factor should be larger when toxicity is severe or when a notification relies on studies with limited duration or small populations.

- Uf_{inter}: Extrapolation from animal to human requires an uncertainty factor for *interspecies* variation: A factor of 10 is usually used to capture the uncertainty associated with using chronic animal studies to predict the safety of chronic human exposure. A factor of 10 can also be used to account for the uncertainty of using sub-chronic animal studies to predict the safety of sub-chronic (including intermittent) human exposure.

- Uf_{extrap}: Extrapolating from a set of two sub-chronic toxicity studies in different animal species to chronic exposure in humans is not recommended, but the associated uncertainty may be approximated by an additional safety factor of 10 to account for the use of sub-chronic data to predict chronic use. If sub-chronic toxicity data are available in only a single animal species, an additional safety factor should be used. Usually, this additional safety factor should be approximately 2.

6. **Does FDA recommend including margin of safety discussions in NDI notifications?**

Yes. To conclude that a dietary supplement containing a NDI will reasonably expected to be safe, it is necessary to determine the margin of safety between the level of the NDI shown to cause no observed adverse effects (the NOAEL) in each animal and/or human study and the intake level that would result from the proposed conditions of use of the NDI in the dietary supplement. The margin of safety is calculated by dividing the NOAEL (not the NOEL) in animal or human studies by the EDI of the NDI. If you are calculating a margin of safety for a combination of ingredients or for the finished dietary supplement, the same principles apply. While the discussion of the difference between a NOEL and a NOAEL may be relevant to a particular study or comprehensive safety profile, because of its importance to the overall safety evaluation the discussion should be placed in the dietary supplement Safety Narrative.

7. **What is the difference between a safety factor and a margin of safety?**

Safety factors are used to account for uncertainty about the extent to which data gathered in one context can be used to predict the safety of a substance in other contexts.For example, safety factors attempt to account for differences between animals and humans and differences in sensitivity among humans. The use of safety factors is based on the observation that toxic substances usually have thresholds below which toxic effects cannot be detected. Safety factors are used in calculating an acceptable daily intake (ADI) for various FDA-regulated products, including color additives, food additives, and new animal drugs. Safety factors can be combined multiplicatively to predict toxicity in the human population.

- ADI (Acceptable Daily Intake) = NOAEL/combined safety factors

- Margin of safety = NOAEL/EDI

In contrast, the margin of safety is a calculation derived from the NOAEL in a single study and the highest total daily intake level determined from the conditions of use in the NDI notification, the EDI. A margin of safety is a measure of how close the estimated daily intake (EDI) is to the level that has been shown to have no adverse effect in animal or human studies (the NOAEL). When reviewing notifications, FDA intends to calculate the EDI based on the highest daily intake level that is possible under the conditions of use proposed in the notification as well as cumulative exposure from all dietary sources. The margin of safety for a dietary ingredient is calculated by dividing the NOAEL in animal or human studies by the EDI of the dietary ingredient. So a margin of safety of 100-fold means the doses shown to be without adverse effects in animals or humans are 100 times greater than the levels that would be consumed from the use of the dietary supplement. Discussions of how ADIs and EDIs are calculated and used in safety evaluations for a variety of products can be found in the following references:

- Frankos, V.H., and J.V. Rodricks. Food additives and nutrition supplements. Regulatory Toxicology, 2nd Ed., S.C. Gad, ed. London: Taylor and Francis; 2001.

- World Health Organization. International Programme on Chemical Safety. Geneva, Switzerland. 1987. Environmental Health Criteria 70: Principles for the safety assessment of food additives and contaminants in food.

- NAS National Academy of Sciences. Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients. 1998. Food and Nutrition Board, Institute of Medicine. Washington DC, National Academies Press.

Example: The only safety evidence available is a single sub-chronic rat study during which no adverse effects were noted at the highest dose, which was the maximum tolerated dose of 3,000 mg/kg body weight. The top dose was limited by the fact that larger volumes could not be humanely administered to the animals. If the proposed conditions of use for the ingredient are 1 mg/person per day in adults daily, the EDI is (1 mg/person)/70 kg average adult = 0.014 mg/kg. The margin of safety is 3,000/0.014 =2.1×10^5. The safety factors chosen are $Uf_{intra} \times Uf_{extrap} \times Uf_{inter}$ =10×10×20 = 2000. The ADI is 3,000/2,000 = 1.5 mg/kg. The EDI/ADI ratio is 0.014/1.5 = 0.01.This value is much less than one, which suggests that, if these safety factors are appropriate, the test article may reasonably be expected to be safe at the proposed daily intake level. An intake level of 1g per day (1000 times greater) would result in an EDI/ADI ratio of close to 10. More studies would be needed to justify the higher serving level.

8. **When is the ratio of the EDI to the ADI adequate to support the conclusion that a dietary supplement containing a NDI will reasonably be expected to be safe?**

   The ratio of the Estimated Daily Intake (EDI) to the Acceptable Daily Intake (ADI) should be less than or equal to 1 to support a conclusion that the proposed use of the NDI in the dietary supplement will reasonably be expected to be safe under the conditions recommended or suggested in the supplement's labeling. The size of the EDI/ADI ratio will vary in accordance with the nature and extent of data available and the circumstances of use of the NDI. For example, a ratio of one, where the proposed dose (EDI) is equal to the safe dose (ADI), could be adequate if the levels of historical chronic safe use of the ingredient are the same as the levels proposed in the dietary supplement.

   Stated another way, the Estimated Daily Intake (EDI) of the NDI must be less than or equal to the Acceptable Daily Intake (ADI) of the NDI or dietary supplement.

   The EDI for the NDI or for the dietary supplement is the top total daily intake level under the proposed conditions of use described in the notification. The ADI is calculated as the ratio of the NOAEL to the combined safety factor, which is calculated by multiplying the individual safety factors for each study. If the ratio of the EDI to the ADI is greater than unity (EDI/ADI > 1), then the study does not support a reasonable expectation of safety for the NDI under the proposed conditions of use.

9. **What is an example of a common error about margin of safety in NDI notifications that have been submitted to FDA for review?**

   Many manufacturers or distributors assume that if the NDI has a history of safe use in humans, no further safety discussion is warranted. That is incorrect. A margin of safety for NDI intake should be calculated, and the method of calculation explained and justified in the notification, even if a history of safe use is the basis of the safety evaluation. When the notification relies on a history of safe use, a margin of safety should be calculated based upon the historical levels of the NDI that were safely consumed and the NDI intake levels that would result from the conditions of use proposed in the notification. A margin of safety of one (or less than one) corresponds to the argument that a history of safe use alone is sufficient to demonstrate the safety of the proposed use based on conditions of use that are the same or lower, respectively, than the conditions of historical use (see question VI.B.14).

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VII. DEFINITIONS

The following definitions represent FDA's current thinking on the meaning of the terms below in the context of the new dietary ingredient provisions of the Act and regulations. The definitions are intended for use only in that context and may not be appropriate in other contexts.[49]

Acceptable Daily Intake (ADI):
The daily intake of a NDI or dietary supplement containing the NDI that, during the human lifetime, appears to be without appreciable risk (affects 1 in 1 million people or less) on the basis of all known facts at the time. It is calculated as the ratio of the NOAEL to the total safety factor (determined from the studies submitted in the notification).[50]

Amino acid:
An alpha-amino carboxylic acid used as a constituent of proteins or peptides.[51]

Botanical or Herbal:
A plant, alga, or fungus; a part of a plant, alga, or fungus (e.g., bark, leaves, stems, roots, flowers, fruits, seeds, berries, or parts thereof); or an exudate (secretion) of a plant, alga, or fungus.

Botanical Raw Material:
Whole or physically processed (e.g., cleaned, frozen, dried, or sliced) parts of a single species of plant or a fresh or processed alga or fungus.

Chemically altered:
See question IV.B.4.

Chronic:
In the context of historical use by humans (i.e., outside of controlled studies), refers to daily lifetime use. In the context of animal and human studies, refers to studies with a duration of one year or longer.

Component:
A substance that is part of a mixture. Includes substances that cannot be isolated from the whole, as well as those that can. Once isolated, a component of a mixture is also a constituent (see definition below).

Concentrate:
An article in which constituents are more concentrated than the original. An herbal concentrate is an extract from which all or most of the solvent has been removed, reducing the product to a solid, semi-solid or syrupy form. The solvent and the process by which the concentrate is made are part of the definition of the concentrate.

Configurational isomer:
See **Stereoisomers**.

Constituent:
An article that is a physical part of the whole and can be isolated from the whole.

Dietary ingredient:
A dietary ingredient is (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 (A) through (E).[52]

Dietary substance:
A substance that is commonly used as human food or drink.

Enantiomers:
Mirror-image isomers that have different chemical, physical, and biological properties.

Estimated Daily Intake (EDI):
For a dietary supplement, the highest total daily intake level (in mg/day) or dose (in mg/kg/day), as determined from the proposed conditions of use in the notification. It is the maximum amount that would be consumed based on the conditions of use proposed and recommended in the notification and should take into account cumulative exposure from other dietary sources. The EDI should not be higher than the ADI.

Extract:
A product consisting of a solvent (menstruum) combined with a dietary substance or botanical biomass by a process that physically separates constituents from the dietary substance or botanical and dissolves them into the solvent. The extract can be further concentrated through drying to a dry powder or semi-solid form.

Formulation:
A formula that (1) lists the identity and quantity of each dietary ingredient and other ingredients (formulation aids) of a dietary supplement, and (2) describes the administered form (e.g. powder, liquid, capsule, etc.).

Geometric isomers:
Compounds that have the same molecular formula, but differ from each other in the way that the atoms are oriented in space, and therefore have different chemical, physical and biological properties (unless interconverted in the gut).

Ingestion:
Taking an article, such as a dietary supplement or other food, into the stomach and gastrointestinal tract by swallowing.

Live microbial dietary ingredient:
A single-celled prokaryotic or eukaryotic microorganism that is intended to be viable at the point of ingestion.

Marketed:
See question IV.A.6.

Margin of safety:
A measure of how close the estimated daily intake (EDI) is to the level that has been shown to have no adverse effect in animal or human studies (the NOAEL). It is calculated as the ratio of the NOAEL to the highest total daily intake level (EDI) of the NDI or dietary supplement, as determined from the proposed conditions of use in the NDI notification.

Maximum tolerated dose (MTD):
The dose that causes no more than a 10% reduction in body weight and does not produce mortality, clinical signs of toxicity, or pathologic lesions that would be predicted to shorten the natural life span of an experimental animal for any reason other than the induction of neoplasms. [53]

Metabolite:
A metabolite of a dietary ingredient is a molecular intermediate that incorporates structural elements of the ingested dietary ingredient and whose flux or net production in the human body increases on ingestion of the dietary ingredient. A metabolite can be part of (or an intermediate of) the catabolic or metabolic pathway of a dietary ingredient. FDA considers X to be a metabolite of Y if ingestion of Y by humans results in net production of/increased flux of X, incorporating structural elements of Y. [54]

Mineral:
A substance of defined chemical composition which provides a form or source of inorganic elements to the diet. An element is any class of substances, such as calcium, iodine, or zinc, which cannot be separated into simpler substances by chemical means.

Nanomaterial, Nanotechnology:
FDA has not adopted a formal definition of "nanotechnology," "nanomaterial," "nanoscale," or related terms. In the absence of a formal definition, when considering whether an FDA-regulated product, including dietary ingredients, contains nanomaterials or otherwise involves the application of nanotechnology, FDA intends to ask: 1.Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or 2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.[55]

New dietary ingredient:
A dietary ingredient that was not marketed in the U.S. before October 15, 1994.[56]

No-Observable-Effect Level (NOEL):
The highest dose or total daily intake level at which no effects (beneficial, neutral, or adverse) are observed in a properly designed and executed toxicological study.

No-Observed-Adverse-Effect Level (NOAEL):
The highest dose or total daily intake level that did not elicit an adverse effect in a properly designed and executed toxicological study.[57]

Pre-DSHEA dietary ingredient:
A dietary ingredient that was marketed in the U.S. before October 15, 1994.

Safety Factor or **Uncertainty Factor:**
A multiplier used to account for uncertainty about the extent to which data gathered in one context can be used to predict the safety of a substance in other contexts. For example, safety factors attempt to account for differences between animals and humans (uncertainty factor of interspecies variation), differences in sensitivity among humans (uncertainty factor of intraspecies variation), and extrapolation of sub-chronic to chronic data (uncertainty factor of extrapolated data from sub-chronic to chronic). Safety factors can be combined multiplicatively to account for multiple sources of uncertainty. Safety factors are used in calculating an acceptable daily intake (ADI) for various FDA-regulated products, including color additives, food additives, and new animal drugs. See VI.C.5 and VI.C.7.

Salt of a dietary ingredient:
Salts are composed of cations (positively charged ions) bound to anions (negatively charged ions). The salt of a dietary ingredient is a neutral compound that is formed by the union of an acid or a base with a counter ion and that dissociates to the starting ingredients after ingestion.

Stereoisomers:
Stereoisomers are molecules that are identical in atomic composition and bonding, but differ in the three-dimensional arrangement of the atoms.

Sub-chronic:
Refers to intermittent use that is either daily and finite in duration, or less than daily throughout the lifetime (i.e., use that is less than chronic). For example, a 90-day sub-chronic study in rodents whereby a dietary supplement is fed daily for a finite period of 90 days is a sub-chronic study. See question VI.B.6.

Target Population:
The target population for a dietary supplement means the population group or groups (defined by gender, age, and/or health status) that a manufacturer or distributor identifies (e.g., in product labeling, promotional materials, or in a NDI notification) as those for whom the product is appropriate or recommended. Examples of target populations include adults, children 14 and over, and women going through menopause.

Tincture:
An aqueous alcoholic solution (e.g., an aqueous alcoholic extract of leaves or other plant material). A tincture is characterized by the ratio of the weight of the dried botanical to the volume or weight of the finished product. A 1:5 ratio is one part botanical to 5 parts alcohol.

Uncertainty Factor:
See **Safety Factor**.

Vitamin:
An organic substance that is a minor component of foods, is essential for normal physiological functions (e.g. maintenance, growth, or development), is normally not produced endogenously (within the body) in amounts adequate to meet normal physiologic needs, and which causes, by its absence or underutilization, a clinically defined deficiency syndrome.

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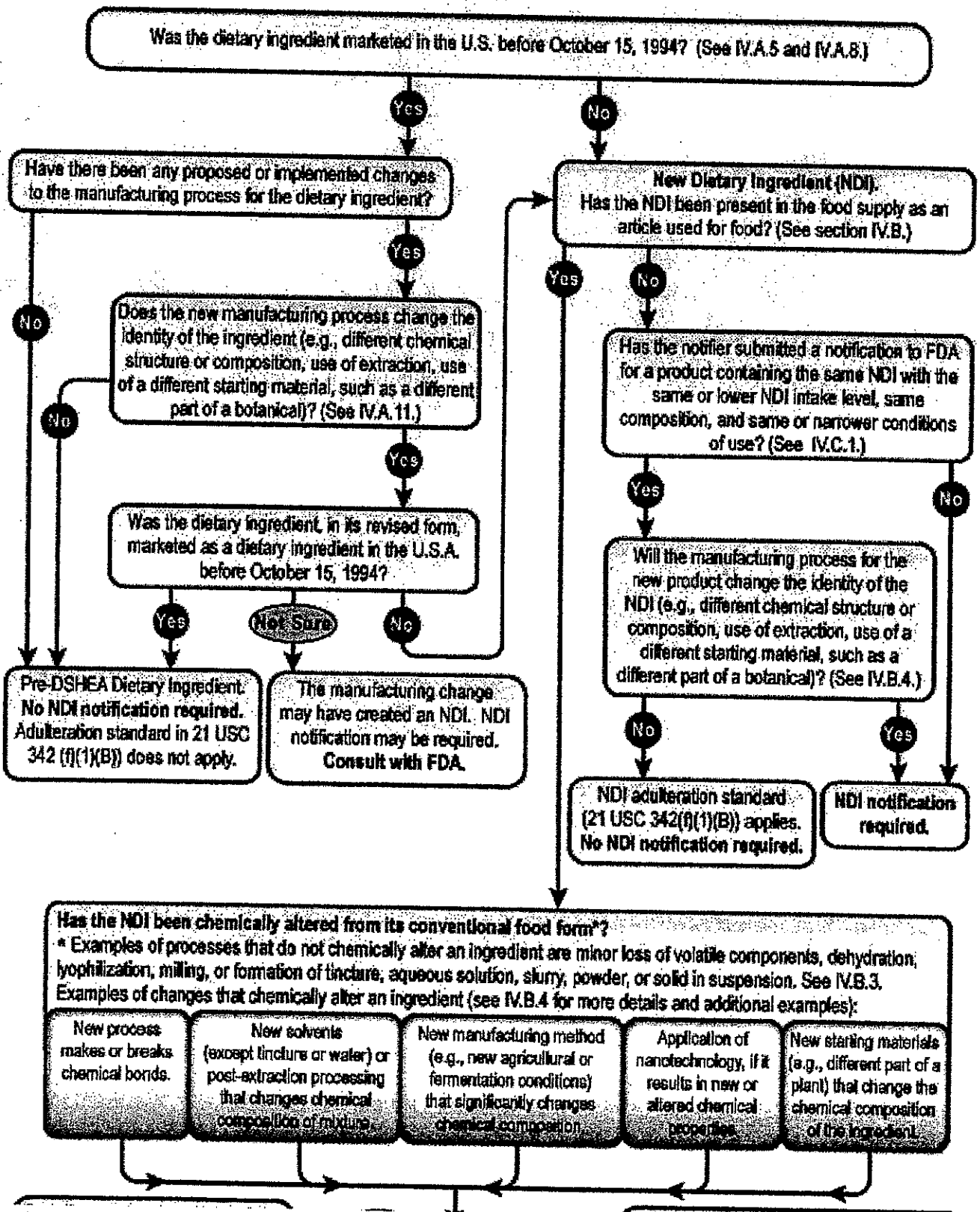
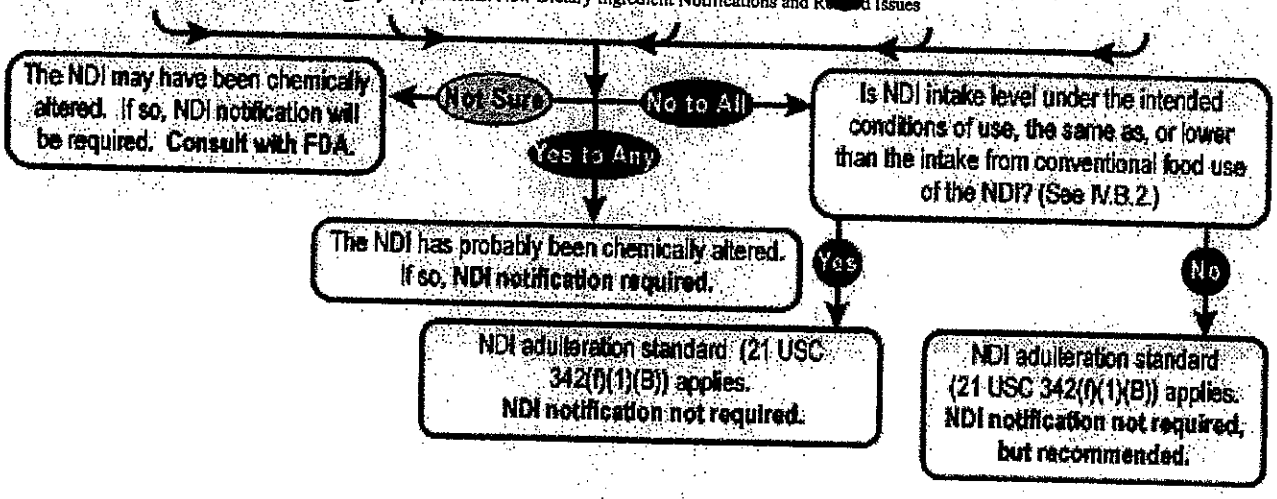
VIII. APPENDICES

Appendix A: Decision Tree for NDI Notification[58]





Text description
Printable PDF

Appendix B: 75-Day Pre-Market New Dietary Ingredient Notification Form

Below is a non-fillable image of the fillable PDF form. The fillable pdf form is available.

Department of Health and Human Services
Food and Drug Administration

75 DAY PRE MARKET NEW DIETARY INGREDIENT (NDI) NOTIFICATION

Version : 2.1

Form Approved: OMB No. xxxx-xxxx Expiration Date: mm/dd/yyyy
Draft for Test Only (See last page for OMB Statement)

FDA USE ONLY

NDI Number | AIMS Number

Date of Receipt

PART I - INTRODUCTORY INFORMATION ABOUT THE NOTIFICATION

1. Type of Notification (Complete a. or b. below)

☐ New Dietary Ingredient

Transmit completed form and attachments in paper format or on physical media to: Office of Nutrition Labeling and Dietary Supplements (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835

b. If Additional Information/Incoming Correspondence, check one of the following:

☐ Amendment ☐ Correspondence (ID, CCI) ☐ Correspondence, Others

Enter the appropriate number(s) applicable to this update or amendment.

NDI Number

2. ☐ All electronic fields included in this notification have been checked and found to be virus free. (Check box to verify)

3a. For New Notifications only: Enter the date of most recent premotification consultation (if any) with FDA on the subject substance (yyyy/mm/dd):

3b. For Amendments only: Is your amendment submitted in response to a communication from FDA? (Check one) ☐ Yes ☐ No If Yes, enter the date of communication (yyyy/mm/dd):

PART II - [illegible]

Name of Contact Person | Position

Company (if applicable)

Mailing Address (number and street)

City | State or Province | Zip Code/Postal Code | Country

Telephone Number | Fax number | E-Mail Address

	Name of Contact Person		Position
	Company (if applicable)		
	Mailing Address (number and street)		
City	State or Province	Zip Code/Postal Code	Country
Telephone Number	Fax number	E-Mail Address	

Add Continuation Page

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Save Page | Print Page | Export Data | Import Data | Next Page | Previous Page | Clear Page(s) | Reset Form | Save Form

PART III - GENERAL ADMINISTRATIVE INFORMATION

1. Title of Notification/Name of New Dietary Ingredient(s)

2. Notification Format *(Check appropriate box(es))*

☐ Paper ☐ Electronic files on physical media with paper signature page

If applicable, give number and type of physical media.

3. For paper notifications only

Number of Volumes: _____

Total number of Pages: _____

Total number of Copies: _____

5. Previous notification(s). *(Check all that apply)*

☐ a) Previous notification(s), same notifier: NDI No. _____, _____, _____

FDA use only

☐ b) Related Notifications from other notifiers NDI No. _____, _____, _____

☐ c) No previous notification with this NDI

☐ d) Other information (briefly describe)

6. Have you designated information in your notification that you view as trade secret or as confidential commercial or financial information? *(Check one)*

☐ Yes, see attached designation of confidential information

☐ Yes, information is designated at the place where it occurs in the notification ☐ No

7. Have you attached a redacted copy of some or all of the notification? *(Check one)*

☐ Yes, redacted copy of complete notification

☐ Yes, redacted copy of part(s) of notification ☐ No

8. Are all citations to published information accompanied by reprints or full photostatic copies of the publication? (Check one) ☐ Yes ☐ No

9. Are published materials all in English or a complete and accurate translation provided? *(Check one)* ☐ Yes ☐ No

10. Have you described the dietary supplement that contains the new dietary ingredient? *(Check one)* ☐ Yes ☐ No

PART IV.A - NEW DIETARY INGREDIENT NAME(S)

New Dietary Ingredient Type *(Check all that apply)* - 201(ff)(1)(A-F)

☐ A. Vitamin ☐ B. Mineral ☐ C. Herb/Botanical ☐ D. Amino Acid ☐ Not a Dietary Ingredient ☐ To Be Determined

☐ E. A dietary substance to supplement the diet

☐ F. A concentrate, metabolite, constituent, extract or combination of any ingredient described above

Level of this new dietary ingredient in each serving of the dietary supplement product

NDI Name

NDI Name:

Synonyms/Trade Name:

Plant Part/Strain :

Latin Binomial Name (LBN):

Author of LBN:

Add Continuation Page

Serving Form (Check all that apply):

☐ Tablet ☐ Capsule ☐ Powder ☐ Softgel

☐ Liquid ☐ Gelcap ☐ Other

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Save As... Print Export Data Import Data Next Page Previous Page Go to Page # Reset Form Submit Form

Description of dietary supplement product (include level of the NDI and all other ingredients in the dietary supplement).

Serving instructions (include total daily intake level)

Conditions of use (Serving size, # of servings/day, serving instructions, and duration of use).

Target and/or excluded populations/other restrictions

Other	

Clear All | Print | Export Data | Import Data | Add Page | Previous Page | Go To Page | Submit Form | Next Page

PART V - COMPOSITION OF THE DIETARY SUPPLEMENT PRODUCT
(including all constituents)

Note: Abbreviations for Chemical Classifications: NDI (New Dietary Ingredient), DI (dietary ingredient that is not an NDI). List non-dietary ingredients as either GRAS (Generally Recognized as Safe for their intended use), FAP/CAP (approved food or color additives), C (other constituent including marker compounds), I (impurity/contaminant e.g. toxicants, residual solvents, pesticides, pathogens, heavy metals).

Chemical Classification/ Function	Chemical Name	CAS® Registry Number	Trade Name (if any)	Link To Chemical Structure/Spectrum/ Chromatogram.
				Go To Link
				Go To Link
				Go To Link
				Go To Link
				Go To Link

				Go To Link
				Go To Link

* CAS = Chemical Abstracts Service

Add Continuation Page

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PART VI - Other Supporting Information in the Notification Which Could be Useful to Determine Identity or Safety of the NDI (Check the boxes below to [illegible] submission [illegible]. Check all that apply.)

1. ☐ Administrative
   - 1.1 ☐ Designation of Nondisclosable information
   - 1.2 ☐ Redacted document
   - 1.3 ☐ If additional information or correspondence, check all that apply.
     - 1.3.1 ☐ Amendment
     - 1.3.2 ☐ Correspondence
   - 1.4 ☐ Safety Narrative
2. ☐ Chemistry/Identity
   - 2.1 ☐ Detailed description of ingredients and product
   - 2.2 ☐ Manufacturing Methods
   - 2.3 ☐ Specifications
     - 2.3.1 ☐ Dietary Ingredients
     - 2.3.2 ☐ Other Ingredients
     - 2.3.3 ☐ Dietary Supplement
     - 2.3.4 ☐ Analytical Methods
     - 2.3.5 ☐ Certificates of Analysis
   - 2.4 ☐ Studies (Check all that apply)
     - 2.4.1 ☐ Composition
     - 2.4.2 ☐ Fingerprint/Markers
     - 2.4.3 ☐ Describe how the constituents of complex mixtures are standardized from batch to batch and how adulterants are excluded
     - 2.4.4 ☐ Stability/shelflife
     - 2.4.5 ☐ Dissolution/absorption
     - 2.4.6 ☐ Other studies
   - 2.5 ☐ References (Identity)
     - 2.5.1 ☐ Cited Literature (published)
     - 2.5.2 ☐ Cited Literature (unpublished)
3. ☐ Safety
   - 3.1 ☐ Comprehensive Safety Profile(s)

3. Safety *(Continued)*
   - 3.2 Toxicology Studies *(Continued)*
     - 3.2.8 ☐ Carcinogenicity Studies: Rodents
     - 3.2.9 ☐ Reproductive Studies
     - 3.2.10 ☐ Developmental/Teratology Studies
     - 3.2.11 ☐ Immunotoxicity Studies
     - 3.2.12 ☐ Metabolism (ADME) and Pharmacokinetic Studies
     - 3.2.13 ☐ Neurotoxicity Studies
     - 3.2.14 ☐ Ingredient Interaction Studies
     - 3.2.15 ☐ Molecular Biology/Genetic Studies
     - 3.2.16 ☐ Antibiotic Resistance/Genetic Stability Studies
   - 3.3 ☐ Human Studies
     - 3.3.1 ☐ Clinical trials primarily designed to study safety
     - 3.3.2 ☐ Clinical efficacy trials
     - 3.3.3 ☐ Adverse Event Reports (including Periodic Safety Update Reports, if any)
   - 3.4 ☐ Other Studies
   - 3.5 ☐ History of Use
     - 3.5.1 ☐ Identity and description of substances that contained the NDI
     - 3.5.2 ☐ How are these substances qualitatively and quantitatively similar to the NDI
     - 3.5.3 ☐ Estimate the historical consumer exposure to these substances (serving level, duration, frequency)
     - 3.5.4 ☐ Monitoring of exposed populations: adverse event reporting/periodic safety update reporting
     - 3.5.5 ☐ Monitoring of exposed populations: other
   - 3.6 ☐ Other Evidence of Safety

3. ☐ Safety
   - 3.1 ☐ Comprehensive Safety Profile(s)
   - 3.2 ☐ Toxicology Studies
     - 3.2.1 ☐ Genetic Toxicity Studies
     - 3.2.2 ☐ Short Term Toxicity Studies: Rodents
     - 3.2.3 ☐ Short Term Toxicity Studies: Non-Rodents
     - 3.2.4 ☐ Subchronic Toxicity Studies: Rodents
     - 3.2.5 ☐ Subchronic Toxicity Studies: Non-Rodents
     - 3.2.6 ☐ One-Year Toxicity Studies
     - 3.2.7 ☐ Chronic Toxicity or Combined Chronic Toxicity/Carcinogenicity Studies: Rodents

   - 3.7 ☐ References
     - 3.7.1 ☐ Literature Publications
     - 3.7.2 ☐ Other (including unpublished, etc)

4. ☐ Other (information in original notification that does not fall under any of the above categories)

5 ☐ Complete reference list for notification

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Notes:

[1] This guidance has been prepared by the Office of Nutrition, Labeling and Dietary Supplements in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] Dietary Supplement Labeling Requirements and Recommendations under the Dietary Supplement and Nonprescription Drug Consumer Protection Act, 74 FR 8262 (Feb. 24, 2009).

[3] Institute of Medicine, Food and Nutrition Board; National Research Council, Board on Life Sciences. Dietary Supplements: A Framework for Evaluating Safety. Washington, DC: The National Academies Press; 2004 Apr.

[4] Letter from Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, to Dietary Supplement Manufacturers (Dec. 15, 2010).

[5] FDA Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat. 3886 (2011).

[6] 21 U.S.C. 350b(c).

[7] Under 21 U.S.C. 342(f)(1)(B), a dietary supplement containing a NDI is adulterated unless there is adequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury.

[8] See, e.g., National Nutritional Foods Association, NNFA List of Dietary Supplement Ingredients In Use Before October 15, 1994 (April 26, 1996). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0012].

[9] Council for Responsible Nutrition, CRN List of Dietary Ingredients "Grandfathered" Under DSHEA (September 1998). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0010].

[10] Statement of Agreement, 140 Cong. Rec. S14801 (daily ed. Oct. 7, 1994).

[11] Statement of Agreement, 140 Cong. Rec. S14801 (daily ed. Oct. 7, 1994).

[12] Adulteration standard 21 U.S.C. 342(f)(1)(B) (section 402f(1)(B) of the FD&C Act): A food shall be deemed to be adulterated if it is a dietary supplement or contains a dietary ingredient that is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.

[13] Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 FR 6788, 6793 (Feb. 11, 2004).

[14] *Pharmanex v. Shalala*, 221 F.3d 1151, 1154-1160 (10th Cir. 2000).

[15] Under 21 CFR 316.3(b)(2), "active moiety" means "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." See also 21 CFR 314.108(a).

[16] Letter from Michael A. Chappell, Acting Associate Commissioner of Regulatory Affairs, FDA, to Kathleen M. Sanzo, Morgan, Lewis & Bockius LLP, responding to Citizen Petition 2005P-0259 from Biostratum, Inc. (Jan. 12, 2009). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0004].

[17] *See Pharmanex v. Shalala*, 2001 WL 741419, at *4 & n.5 (D. Utah March 30, 2001).

[18] *Id.* at *3.

[redacted]

[19] The regulation governing these notifications is 21 CFR 101.93. Please refer to this regulation for instructions on where and how to submit a notification of a dietary supplement labeling claim under 21 U.S.C. 343(r)(6). Notifications for labeling claims are not reviewed by the same staff that review NDI notifications.

[20] *National Parks & Conservation Ass'n v. Morton*, 498 F.2d 765 (D.C. Cir. 1974).

[21] McNeill, J.; Barrie, F.R.; Burdet, H.M. et al., editors. International Code of Botanical Nomenclature (Vienna Code) (electronic ed.) Vienna: International Association for Plant Taxonomy; 2006.

[22] Lapage, S. P.; Sneath, P. H. A.; Lessel, E. F.; Skerman, V. B. D.; Seeliger, H. P. R.; Clark, W. A., editors. International Code of Nomenclature of Bacteria (Bacteriological Code), 1990 Revision. Washington (DC): American Society for Microbiology Press; 1992.

[23] Bacterial Nomenclature Up-to-Date (German Collection of Microorganisms and Cell Cultures Database). Braunschweig, Germany: Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH; cited May 10, 2011. [Note that content on this website is updated frequently. Use the search function in the embedded link to retrieve the current validated name of a bacterial organism.]

[24] Euzéby, J. P., editor. List of Prokaryotic Names with Standing in Nomenclature (LPSN) Database (formerly List of Bacterial Names with Standing in Nomenclature (LBSN)). [Note that content on this website is updated frequently. Use the search function in the embedded link to retrieve the current validated name of a bacterial organism.] Toulouse (France): Editorial Board of the International Journal of Systematic and Evolutionary Microbiology (IJSEM) and the International Committee on Systematics of Prokaryotes (ICSP); cited May 10, 2011.

[25] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry: Estimating Dietary Intake of Substances in Food; August 2006.

[26] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions; March 2006; revised March 2009.

[27] See, e.g., the definition proposed in the European Union: "[H]istory of safe food use in a third country" means that the safety of the food in question is confirmed with compositional data and from experience of use and continued use for at least 25 years in the customary diet of a large part of the population of a country. *Official Journal of the European Union* C 122 E (Nov. 5, 2010); p. 38 - 57.

[28] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[29] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[30] Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects (electronic ed.). Netherlands: OECD iLibrary; cited May 12, 2011.

[31] U.S. Environmental Protection Agency (EPA), Office of Chemical Safety and Pollution Prevention (OCSPP). OCSPP Harmonized Test Guidelines; April 2010.

[32] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Safety Guidelines. Geneva: ICH; cited May 12, 2011.

[33] Dearfield KL, Thybaud V, Cimino MC, Custer L, Czich A, Harvey JS, et al. Follow-up actions from positive results of in vitro genetic toxicity testing. Environ Mol Mutagen. 2011 Apr;52(3):177-204.

[34] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety.Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[35] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety.Subchronic Toxicity Studies. In: Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[36] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 408: Repeated Dose 90-day Oral Toxicity Study in Rodents. Netherlands: OECD Publishing; May 1981; revised September 1998.

[37] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 415: One-Generation Reproduction Toxicity Study. Netherlands: OECD Publishing; May 1983.

[38] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 416: Two-Generation Reproduction Toxicity Study. Netherlands: OECD Publishing; May 1983; revised January 2001.

[39] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 421: Reproduction/Developmental Toxicity Screening Test. Netherlands: OECD Publishing; July 1995.

[40] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Netherlands: OECD Publishing; March 1996.

[41] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidelines for Reproduction Studies. In: Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[42] U.S. Environmental Protection Agency (EPA), Office of Chemical Safety and Pollution Prevention (OCSPP). OCSPP Harmonized Test Guidelines; April 2010.

[43] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Safety Guidelines. Geneva: ICH; cited May 12, 2011.

[44] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2); June 1993; addendum dated November 2000 incorporated November 2005.

[45] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Premarket Approval. Additional Recommended Studies. In: Draft Guidance: Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Draft Redbook II); 1993.

[46] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Premarket Approval. Human Studies. In: Draft Guidance: Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Draft Redbook II); 1993.

[47] U.S. Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for Industry: M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, Revision 1; January 2010.

[48] Adapted from Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

[49] For example, FDA recognizes that "amino acid" can be defined differently in non-nutritional contexts than in the definition in this section.

[50] Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

[51] Letter from Michael M. Landa, Acting Director, Center for Food Safety and Applied Nutrition, FDA, to Marc Ullman, Ullman, Shapiro & Ullman, LLP, responding to Citizen Petition FDA-2009-P-0298 from OVOS Natural Health Inc. (Feb. 23, 2011). Docket No. FDA-2009-P-0298 [Document ID: FDA-2009-P-0298-0008].

[52] 21 U.S.C. 321(ff)(1).

[53] Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

[54] *See* Hardy, Constance J. (Executive Secretary, Dietary Supplements Subcommittee of the FDA Food Advisory Committee). Summary Minutes of March 25, 2003 Meeting of the Dietary Supplements Subcommittee; College Park, MD; dated June 3, 2003.

[55] FDA recently issued a draft guidance to industry titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology".

[56] 21 U.S.C. 350b(c).

[57] Adapted from Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

[58]The adulteration standard for NDIs can be found in 21 U.S.C. 342(f)(1)(B)(section 402(f)(1)(B) of the FD&C Act).

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EXHIBIT 8

Breaking News on Supplements & Nutrition - North America EU edition

NSF: MHA not a constituent of geranium oil

Interview with Ed Wyszumiala
General manager, Dietary supplements Programs, NSF International

By Stephen Daniells in Anaheim, 14-Mar-2011, duration 3:06

The compound methylhexanamine, or MHA, is not a constituent of geranium oil used in sports nutrition products, despite one study reporting its presence as a constituent, says the general manager of NSF International.

Ed Wyszumiala, general manager of dietary supplements programs at NSF International, told Stephen Daniells that his labs have done their own analysis of geranium oil, and *"methylhexanamine is not found as a constituent in geranium oil"*.

"There is one study that is mainly referred where they're finding it as a constituent of geranium to be methylhexanamine," said Wyszumiala, *"but what we're finding is in all the geranium we've tested, all the geranium samples we've tested, all the products we've tested, geranium does not contain this material."*

"We're getting down to a parts-per- billion screen, and we're not finding it."

The geranium oil issue also represents an opportunity for industry, said Wyszumiala. *"The industry, if they can get out in front of it, this is another spiking and adulteration issue where we're having or a synthetic chemical added for a desired or intended effect,"* he said.

"I think we're starting to see the response from industry on the geranium issue," said Wyszumiala.

Related topics: Industry, Nutritional lipids and oils, Energy & endurance

http://www.nutraingredients-usa.com/Industry/NSF-MHA-not-a-constituent-of-geranium-oil

EXHIBIT 9

NATURAL PRODUCTS INSIDER

AHPA: Review of Research Shows DMAA Not Naturally From Geranium

August 5, 2011

0 Comments

Posted in News, American Herbal Products Association (AHPA), Industry News, Business Operations, Botanicals, Labeling, Label Claims

Print

SILVER SPRING, Md.—Members of the **American Herbal Products Association** (AHPA) will no longer be able to label 1,3-dimethylamylamine as geranium oil or as any part of the geranium plant, according to a trade requirement approved by the board of trustees at last month's meeting. While this ingredient, also know by a number of synonyms, has been listed on product labels as derived from geranium oil, stem or extract, AHPA said a critical review of the scientific literature determined no credible evidence showed the constituent is found in geranium species (Pelargonium spp.).

The trade requirement becomes effective on Jan. 13, 2012. Nothing in the new requirement prevents labeling of any compound that is in fact derived from geranium plant materials by that compound's common or usual name.

1,3-Dimethylamylamine, also known as DMAA; 1,3-dimethylpentylamine; methylhexaneamine (MHA); methylhexanamine; methylhexamine; 4-methyl-2-hexanamine; and 2-amino-4-methylhexane, was an inhaled nasal-decongestant drug synthesized by Eli Lilly and Company in 1971 and known as Forthane. More recently, DMAA has been used in dietary supplements for weight loss and bodybuilding.

AHPA said it is sometimes referred to as geranamine due to a single report from a report in a technical institute journal, not a reputable, peer-reviewed journal of chemistry, that found DMAA was a naturally occurring essential oil distilled from geranium leaf. That study, by Ping et al. (*Journal of Guizhou Institute of Technology* 1996;(25)82-85), which identified the presence of DMAA in geranium, described a gas chromatography-mass spectrometry (GC-MS) analysis of essential oil obtained from steam distilling the minced, air-dried leaf of fresh *Pelargonium graveolens*. More than 40 compounds were reportedly detected, and 31 of them were assigned identities based on automatic computer matching to a MS spectral library.

However, AHPA said several problems have been noted with this report. A review of the chromatogram from the original paper, for example, revealed an inadequate separation of compounds for MS-library matches. Other issues with this report include significant concerns over the experimental conditions, the interpretation of data, the quality of data reporting, and the validation of findings.

"After a critical review of the existing scientific literature, and working with John Travis, manager of clinical operations for NSF International and the AHPA analytical laboratories committee, we're quite clear that this reported finding of DMAA from geranium is not scientifically valid," said Steven Dentali, AHPA's chief science officer. "There are no known-published reports indicating that this is a natural product. Any labeling stating that it is naturally occurring in geranium, or any other natural source, would need appropriate scientific evidence to support it. None has yet been found in the public domain."

Also at its July meeting, the board approved the appointment of John Doherty and Bill Carter, Esq., as co-chairs of the AHPA Sports Nutrition Committee. Doherty is director of regulatory affairs for **Iovate Health Sciences**, Ontario, Canada.Carter is general counsel for Bodybuilding.com, Meridian, ID. Doherty and Carter replace Erica Stump, Esq., formerly of **Bodybuilding.com**, who left the company in early April.

At the July meeting, AHPA also amended its existing **guidance policy on Class 1 solvents.**

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EXHIBIT 10

NUTRA ingredients-usa.com

Breaking News on Supplements & Nutrition - North America

Synthetic geranium still raising industry red flags

By Shane Starling, 22-Feb-2011

Related topics: Phytochemicals, plant extracts, Energy & endurance, Weight management, Industry, Quality control

An unauthorized synthetic form of geranium oil – known as 1.3-dimethylpentylamine – remains on-market in major-label dietary supplements, although a retailer crackdown has some *"fringe"* supplement manufacturers looking for other stimulants to illegally boost product efficacy.

One industry observer said with some retailers refusing to sell products containing 1.3-dimethylpentylamine, other unauthorized herbal extracts and their synthetic cousins are gaining prominence with unscrupulous supplement makers.

These include Salvinorin A (derived from from *Salvia divinorum*), mitragynine (from *Mitragyna speciosa*) and nuciferin. All tend to end in weight loss products or those aimed at the body building market. They are also used in 'herbal high' products.

Industry members are especially concerned that consumption of these potent stimulants may lead to serious injury or death as was the case with ephedra before it was banned by the FDA under the 1994 Dietary Supplements and Health Education Act (DSHEA) in 2003.

"Retailers seem to be clamping down on 1.3-dimethylpentylamine ," said one industry observer. *"As a result everyone is desperately seeking the next 'jack me up' compound as the replacement."*

Despite that observation major retailers like GNC continue to freely sell products containing the ingredient, although it can be difficult to determine if they are geranium extracts or synthetically derived.

One product, called Jack3d, lists an ingredient called '13-Dimethylamylamine (Geranium [Stem])' on the product's webpage that also makes the claim: *"This product produces an intense sensation of drive, focus, energy, motivation & awareness. In addition, it allows for rapid increases in strength, speed, power & endurance."*

That link can be found here.

A GNC spokesperson said product enquiries should be directed at the manufacturer, USP Labs, but that company was unavailable for comment at the time of publication.

USP Labs' own website page for Jack3d – found here – contained a disclaimer that references the ingredient's banned status with some sporting organizations : *"...compounds such as caffeine, creatine & 1,3 dimethylamylamine (also known as methylhexanamine, 2-amino-4-methylhexane & 1,3-dimethylpentylamine – a natural constituent of the geranium flower) may not be allowed by your specific sports organization. It's completely up to the user to get this and any dietary supplement cleared by their organization before using."*

Further information adds: *"Geranium has a long history of being used for many purposes in the food supply. It contains a constituent that may provide a boost to your workouts & help you power through tough set after tough set – always ready to take on the next challenge."*

Increasing concern

Commenting on the subject of economically motivated adulteration (EMA), Mark Blumenthal, the founder and executive director of the American Botanical Council (ABC), said: *"There is increasing concern by some experts that there is significant intentional adulteration – not just contamination – usually inintentional – of numerous dietary ingredients for a variety of economic motivations."*

He said the ABC was working with the American Herbal Pharmacopoeia to produce a 'Botanical Adulterants White Paper' that will, *"list known adulterants and analytical methods to detect them, in the hope of reducing some of this kind of fraud."*

It was expected to be published in the Summer or Fall.

Blumenthal noted that Salvinorin A is, *"a traditional psychoactive plant which has become quite popular and controversial."*

A little after publication of this story, the GNC spokesperson added: *"GNC strictly complies with all applicable statutes and regulations, and requires its vendors to represent and warrant that the products they sell do as well."*

EXHIBIT 11

Patented May 30, 1944

2,350,318

UNITED STATES PATENT OFFICE

2,350,318

AMINOALKANES

Horace A. Shonle and Ronald Hahnemann, Indianapolis, Ind., assignors to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

No Drawing. Application April 9, 1943, Serial No. 482,304

6 Claims. (Cl. 167—65)

This invention relates to aminoalkanes and more particularly to 2-amino-4-methylhexanes.

Ephedrine and amphetamine (1-phenyl-2-aminopropane) have long been employed as vasoconstrictors. Ephedrine is obtained from Ma Huang and is also produced synthetically. Whether derived from natural sources or produced synthetically, the preparation of ephedrine is relatively expensive. Ephedrine and its salts are substantially nonvolatile and, as a result, their methods of application are limited to oral, parenteral, and topical administration. Amphetamine, on the other hand, is volatile, may be inhaled and considerable relief obtained in many cases of congestion of the nasal passage by this mode of administration. Amphetamine, however, has the decided disadvantage of markedly stimulating the central nervous system and is relatively toxic.

The compositions of this invention possess the desirable properties of both ephedrine and amphetamine but do not manifest some of the undesirable characteristics of these two materials. The compositions of this invention are 2-amino-4-methylhexane and the acid addition salts of 2-amino-4-methylhexane. The 2-amino-4-methylhexane may be administered for the treatment of congestion of the nasal passage by inhalation, for it is more volatile than amphetamine. The 2-amino-4-methylhexane and its acid addition salts are substantially less toxic than amphetamine and its acid addition salts. Unlike ephedrine, which inhibits the action of smooth muscles, the compositions of this invention stimulate these muscles. The 2-amino-4-methylhexane and its acid addition salts increase the nasal volume to a greater extent than ephedrine or amphetamine. In addition, 2-amino-4-methylhexane and its salts have a negligible effect on the nervous system and are relatively nontoxic.

Aqueous solutions or solutions in physiological saline of 2-amino-4-methylhexane sulfate up to 4 percent are well tolerated by the human mucosa and produce no subjective discomfort of any kind in the patient. There is a notable absence of local tingling and of subsequent systemic reaction, such as tremor, excitement or insomnia which are some of the more common subjective symptoms produced by ephedrine and its acid addition salts.

The 2-amino-4-methylhexane may be administered topically, while the acid addition salts of 2-amino-4-methylhexane may be administered orally, parenterally, or topically. For topical administration of the 2-amino-4-methylhexane, it may be dissolved in a suitable solvent, such as cottonseed oil or liquid petrolatum, or it may be incorporated in a jelly or ointment, or it may be utilized directly by inhalation. The acid addition salts of the 2-amino-4-methylhexane are preferably dissolved in water or physiological saline solution or a sugar solution, such as glucose. For topical administration, a water solution, such as an isotonic water solution, can be conveniently used, while for parenteral administration physiological saline, an aqueous solution, or an isotonic solution of the desired acid addition salt may be employed. Jellies may also be used for topical administration and may be prepared by incorporating an acid addition salt of 2-amino-4-methylhexane in water, glycerin, and some viscous medium or thickening agent, such as gum tragacanth, sodium alginate or methyl cellulose.

In addition, the 2-amino-4-methylhexane or the acid addition salt of 2-amino-4-methylhexane may be combined with local anesthetic bases. Preferably, an acid addition salt of 2-amino-4-methylhexane is employed with an acid addition salt of the local anesthetic base or the local anesthetic base itself. Such combinations may be used in any suitable form, such as solutions, jellies, or ointments. An especially useful combination is that obtained by incorporating the acid addition salt of 2-amino-4-methylhexane with the acid addition salt of a local anesthetic base in an aqueous solution.

Examples of local anesthetic bases as such or as their acid addition salts for the purposes of this invention are:

Cocaine—methylbenzoylecgonine
Procaine—p-aminobenzoyldiethylaminoethanol
A-(2-methyl-piperidino)-propyl benzoate
p-Amino-benzoyl-dimethylamino-methylbutanol
p-Aminobenzoyl-A-di-n-butylaminopropanol
p-Aminobenzoyl-2-2-dimethyl-3-diethylaminopropanol
Monoisobutylaminoethyl-p-aminobenzoate
Piperidinopropanediol-di-phenylurethane
2-butyloxyquinolinecarboxylic acid-A-diethylethylene-diamine
A-diethylaminopropylcinnamate

The compositions of this invention are prepared by any one of the following methods:

1. One molecular equivalent of 4-methylheptanone-3 is reacted with slightly more than one molecular equivalent of hydroxylamine. Preferably, the hydroxylamine is prepared in the free

ence of the 4-methylhexanone-2 by reacting the hydrochloride or sulfate or other salt of the hydroxylamine with a suitable base, such as sodium carbonate or sodium hydroxide. Desirably, the reaction mixture is agitated for a few hours to insure the conversion of the 4-methylhexanone-2 to 4-methylhexanone-2 oxime. The resulting 4-methylhexanone-2 oxime separates and is dried by any suitable means, such as with a dehydrating agent, for example, sodium sulfate or magnesium sulfate. After drying, 4-methylhexanone-2 oxime is reduced with hydrogen by means of a catalyst, such as Raney nickel, or by reaction of sodium and a primary alcohol, such as ethanol. The resulting 2-amino-4-methylhexane may be purified by distillation.

2. Another method of preparing the 2-amino-4-methylhexane of this invention is to react one molecular equivalent of 4-methylhexanone-2 with approximately four molecular equivalents of formamide or ammonium formate. The mixture is heated to a temperature of 185°–195° C. and maintained at that temperature until the liberation of ammonium carbonate ceases. This condition may be readily ascertained by observing a condenser attached to the reaction mixture. The reaction product is separated from the excess formamide by adding water to the mixture, agitating, and separating the reaction product, which is insoluble in water, from the water solution. The reaction product is then refluxed with an excess of mineral acid, such as concentrated hydrochloric or dilute sulfuric acid. Desirably, the reaction product is refluxed for a period of from one to two hours, during which time the acid addition salt of 2-amino-4-methylhexane is formed. If the base 2-amino-4-methylhexane is desired, the acid addition salt is treated with a suitable base, such as sodium carbonate or sodium hydroxide. If purification is desired, it may be distilled.

3. A third method of preparing compositions of this invention is to subject a quantity of 4-methylhexanone-2 to the action of ammonia and hydrogen in the presence of a suitable catalyst, such as Raney nickel. Desirably, an excess of ammonia and hydrogen is used and the reaction may be conveniently performed in a bomb by dissolving the ammonia in a solvent, such as ethanol.

If acid addition salts of the base, 2-amino-4-methylhexane, are desired, the 2-amino-4-methylhexane is reacted with an equivalent of the desired acid. The reaction is almost immediate and can be carried out in a suitable solvent, such as ethyl ether, ethanol, or water. In this manner the acid addition salts of 2-amino-4-methylhexane may be formed, such as the acetic, hydrobromic, hydrochloric, sulfuric, maleic, propionic, or malonic acid salts of 2-amino-4-methylhexane.

In the preparation of the 2-amino-4-methylhexane or the acid addition salts of 2-amino-4-methylhexane by the methods outlined herein, racemic mixtures of the *d* and *l* forms of 2-amino-4-methylhexane or the acid addition salts of 2-amino-4-methylhexane result. These racemic mixtures may be removed, if desired, by any of the well-known methods and, after resolution, the *d* or the *l* form may be used alone as a vasoconstrictor or for other purposes instead of the racemic mixtures.

Typical examples of the compositions of this invention and the methods of preparing them are as follows:

Example 1.—Preparation of 2-amino-4-methylhexane.

In a 2-liter flask equipped with a stirrer and thermometer is placed 88 g. (0.83 mol) of hydroxylamine hydrochloride and 175 cc. of cold water. This mixture is stirred until solution is complete. To this solution is added 115 g. (1 mol) of 4-methylhexanone-2. The mixture is stirred and a solution of 50 g. (0.5 mol) of anhydrous sodium carbonate in about 150 cc. of water is added through a dropping funnel. This addition is regulated so that the temperature does not rise above 30° C. During this time 4-methylhexanone-2 oxime is formed. The stirring is continued for 1 to 2 hours after the addition is completed. The mixture separates into two layers, a water layer and a water-immiscible layer. The water-immiscible layer, which contains the 4-methylhexanone-2 oxime, is washed with water and dried with magnesium sulfate or sodium sulfate.

A solution of 50 g. of crude dry 4-methylhexanone-2 oxime in 1000 cc. of absolute ethanol is heated to boiling in a 2-liter flask equipped with an efficient reflux condenser. The source of heat is withdrawn and approximately 200 g. of sodium metal is added as rapidly as possible without essential loss of the ethanol. During this time the 2-amino-4-methylhexane is formed. When all of the sodium is added and reacted, the mixture is cooled and diluted with about 1500 cc. of water. The mixture is distilled through an efficient condenser until no more 2-amino-4-methylhexane comes over. The distillate is adjusted to about pH 5 with hydrochloric acid and the solvents removed by heating in vacuum. The residual material is cooled and made alkaline with strong sodium hydroxide solution. The 2-amino-4-methylhexane is separated from the lower water layer and dried first over solid potassium hydroxide and then over magnesium sulfate. The product, which is 2-amino-4-methylhexane, may be distilled as a colorless liquid, B. P. about 131°–133° C. uncorrected.

Example 2.—Preparation of 2-amino-4-methylhexane.

To a mixture of 30 g. of Raney nickel catalyst and 50 g. of 4-methylhexanone-2 contained in a steel bomb is added 170 cc. of cold absolute ethanol which has been saturated with anhydrous ammonia at −5° C. The resulting mixture is shaken for 3 hours with hydrogen at a pressure of 10 to 150 atmospheres at a temperature of 70° to 100° C. The catalyst is removed by filtration and the filtrate subjected to fractional distillation through an efficient fractionating column. The fraction boiling at about 131°–133° C. consists of 2-amino-4-methylhexane.

Example 3.—Preparation of 2-amino-4-methylhexane.

A mixture of 250 g. (4 mols) of ammonium formate and 115 g. (1 mol) of 4-methylhexanone-2 is heated in a 1-liter flask equipped with a thermometer well and an 8-inch Vigreux column. The top of the Vigreux column is connected to a condenser of large bore set for distillation. The mixture is heated from 150° to 185° C. until distillation stops. The ketone which has distilled over is separated and returned to the reaction flask and the heating continued. Water, carbon dioxide and ammonia are formed as by-products in the reaction. The reaction re-

quires approximately 8 to 10 hours to complete. During this time the formyl derivative of 2-amino-4-methylhexane is formed. When the reaction is completed the mixture is shaken with water and the water-insoluble material separated. The water-insoluble material is refluxed with 150 cc. of concentrated hydrochloric acid for about two hours. During this time the hydrochloride of 2-amino-4-methylhexane is formed. The aqueous solution of the hydrochloride after being freed from any unchanged ketone, as by steam distillation, is cooled and made alkaline with strong sodium hydroxide solution. The separated 2-amino-4-methylhexane is dried first with solid potassium hydroxide and then with anhydrous magnesium sulfate. The 2-amino-4-methylhexane is distilled as a colorless liquid, boiling at about 131°-132° C. uncorrected.

In this preparation formamide may be used instead of ammonium formate with good results. As in the case with ammonium formate best results are obtained by using an excess of formamide.

Example 4.—Preparation of 2-amino-4-methylhexane.

A mixture of 97 g. (0.75 mol) of 4-methylhexanone-2 oxime, 100 cc. of ethanol and 2.0 g. of Raney nickel catalyst is shaken with hydrogen at 15 to 150 atmospheres pressure and a temperature of 75°-100° C. for 5 hours. During this time 2-amino-4-methylhexane is formed. The catalyst is removed by filtration and the filtrate subjected to fractional distillation. The material boiling at about 131°-132° C. uncorrected is collected separately and comprises the desired amine, 2-amino-4-methylhexane.

Example 5.—Preparation of 2-amino-4-methylhexane sulfate.

A mixture of 75 g. of 2-amino-4-methylhexane, 200 cc. of absolute ethanol and 240 cc. of aqueous 2N sulfuric acid is evaporated to dryness on a steam bath. During this time the 2-amino-4-methylhexane sulfate is formed. The white solid is powdered and washed on a Buchner funnel first with ethyl ether-ethanol (1:1) and then with dry ethyl ether. The white solid is dried at 60°-70° C. in an air oven. The product, which is 2-amino-4-methylhexane sulfate, does not have a definite melting point. It is very soluble in water and sparingly soluble in absolute ethanol. It contains a molecule of water of crystallization.

Other acid addition salts of 2-amino-4-methylhexane may be formed by reacting the 2-amino-4-methylhexane with the required acid. For example, 2-amino-4-methylhexane-n-hexyl sulfonate may be produced by reacting 2-amino-4-methylhexane dissolved in a suitable solvent, such as ethyl ether, with a solution of n-hexyl sulfonic acid dissolved in ethyl ether. Likewise, 2-amino-4-methylhexane malate, 2-amino-4-methylhexane benzoate, 2-amino-4-methylhexane glycolate, 2-amino-4-methylhexane nicotinate, 2-amino-4-methylhexane maleate, 2-amino-4-methylhexane gluconate, 2-amino-4-methylhexane phosphate, and 2-amino-4-methylhexane succinate may be prepared by reacting 2-amino-4-methylhexane, dissolved in a suitable solvent, with malic acid, benzoic acid, glycolic acid, nicotinic acid, maleic acid, gluconic acid, phosphoric acid, or succinic acid respectively.

Example 6.—Preparation of 2-amino-4-methylhexane inhalant compound.

An effective 2-amino-4-methylhexane inhalant compound is prepared by incorporating the following in approximately 100 cc. of liquid petrolatum:

2-amino-4-methylhexane	g.—	1
Menthol	do—	.75
Camphor	do—	.75
Oil of thyme	cc—	.3
Liquid petrolatum to make	do—	100

Example 7.—Preparation of 2-amino-4-methylhexane sulfate jelly.

An effective 2-amino-4-methylhexane sulfate jelly is prepared by compounding the following ingredients:

	Grams
2-amino-4-methylhexane sulfate	1
Glycerin	10
Tragacanth	1
Methyl salicylate	.01
Sodium phosphate	.2
Water to make	100

Example 8.—Preparation of 2-amino-4-methylhexane ointment.

An effective ointment of 2-amino-4-methylhexane is compounded from the following ingredients:

	Grams
2-amino-4-methylhexane	1
Menthol	.7
Camphor	.7
Oil of wintergreen	.3
Anhydrous wool fat	5
Liquid petrolatum	25
White petrolatum to make	100

Example 9.—Preparation of solution of acid addition salts of 2-amino-4-methylhexane.

An effective solution of 2-amino-4-methylhexane sulfate for use as a nasal spray is compounded from the following ingredients:

Chlorobutanol	g—	.5
2-amino-4-methylhexane sulfate	do—	1
Physiological saline solution	cc—	100

In Examples 7 and 8, acid addition salts of 2-amino-4-methylhexane such as those described in Example 5 may be used instead of 2-amino-4-methylhexane, while in Example 8 oil-soluble acid addition salts such as 2-amino-4-methylhexane oleate may be employed instead of the 2-amino-4-methylhexane. In addition, various other therapeutic compositions may be substituted for the menthol, camphor, methyl salicylate and other ingredients used in the typical Examples 6, 7, and 8. The proportion of all ingredients in these examples may be varied within wide limits, it being understood that these examples are merely typical of a wide variety of solutions, jellies, and ointments which may be prepared with the compositions of this invention.

What is claimed is:

1. A composition selected from the class which consists of 2-amino-4-methylhexane and acid addition salts of 2-amino-4-methylhexane.

2. 2-amino-4-methylhexane.

3. An acid addition salt of 2-amino-4-methylhexane.

4. A solution of a composition selected from the class consisting of 2-amino-4-methylhexane and acid addition salts of 2-amino-4-methylhexane.

5. An isotonic solution of an acid addition salt of 2-amino-4-methylhexane.

6. A 2-amino-4-methylhexane sulfate.

MORACH A. SEROGLE
EWALD BOHRMANN.

EXHIBIT 12

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Mark Drawing Code	(1) TYPED DRAWING
Serial Number	72382454
Filing Date	February 1, 1971
Current Filing Basis	1A
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Registration Number	0925396
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EXHIBIT 13

www.ncbi.nlm.nih.gov/pmc/articles/PMC1929926/pdf/bullnyacadmed00455-0002.pdf

there is no age limit for nasal congestion

[illegible] there are [illegible] when welcome relief is [illegible], treatment with Duramist 'Furthane' (Methylhexanone, Lilly). Suffering from nasal congestion or rhinitis, annoying side-effects from a cold, has often been the case. Since the advent of 'Furthane' effective relief is normally afforded without:

- Possible distortion of [illegible] vibration
- Rise in blood pressure
- Cardiac [illegible]
- Overstimulation followed by secondary congestion and increasing need for relief

For [illegible] as well as relief, physicians are [illegible] Duramist 'Furthane' [illegible] Inhalers. Furthane [illegible]

Detailed [illegible] literature on Duramist 'Furthane' are available through your M S K *

* [illegible]

EXHIBIT 14

Patented May 30, 1944

2,350,318

UNITED STATES PATENT OFFICE

2,350,318

AMINOALKANES

Horace A. Shonle and Ewald Bohrmann, Indianapolis, Ind., assignors to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

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6 Claims. (Cl. 167—65)

This invention relates to aminoalkanes and more particularly to 2-amino-4-methylhexane.

Ephedrine and amphetamine (1-phenyl-2-aminopropane) have long been employed as vasoconstrictors. Ephedrine is obtained from Ma Huang and is also produced synthetically. Whether derived from natural sources or produced synthetically, the preparation of ephedrine is relatively expensive. Ephedrine and its salts are substantially nonvolatile and, as a result, their methods of application are limited to oral, parenteral, and topical administration. Amphetamine, on the other hand, is volatile, may be inhaled and considerable relief obtained in many cases of congestion of the nasal passage by this mode of administration. Amphetamine, however, has the decided disadvantage of markedly stimulating the central nervous system and is relatively toxic.

The compositions of this invention possess the desirable properties of both ephedrine and amphetamine but do not manifest some of the undesirable characteristics of these two materials. The compositions of this invention are 2-amino-4-methylhexane and the acid addition salts of 2-amino-4-methylhexane. The 2-amino-4-methylhexane may be administered for the treatment of congestion of the nasal passage by inhalation, for it is more volatile than amphetamine. The 2-amino-4-methylhexane and its acid addition salts are substantially less toxic than amphetamine and its acid addition salts. Unlike ephedrine, which inhibits the action of smooth muscles, the compositions of this invention stimulate these muscles. The 2-amino-4-methylhexane and its acid addition salts increase the nasal volume to a greater extent than ephedrine or amphetamine. In addition, 2-amino-4-methylhexane and its salts have a negligible effect on the nervous system and are relatively nontoxic.

Aqueous solutions or solutions in physiological saline of 2-amino-4-methylhexane sulfate up to 4 percent are well tolerated by the human mucosa and produce no subjective discomfort of any kind in the patient. There is a notable absence of local tingling and of subsequent systematic reaction, such as tremor, excitement or insomnia which are some of the more common subjective symptoms produced by ephedrine and its acid addition salts.

The 2-amino-4-methylhexane may be administered topically, while the acid addition salts of 2-amino-4-methylhexane may be administered orally, parenterally, or topically. For topical administration of the 2-amino-4-methylhexane, it may be dissolved in a suitable solvent, such as cottonseed oil or liquid petrolatum, or it may be incorporated in a jelly or ointment, or it may be utilized directly by inhalation. The acid addition salts of the 2-amino-4-methylhexane are preferably dissolved in water or physiological saline solution or a sugar solution, such as glucose. For topical administration, a water solution, such as an isotonic water solution, can be conveniently used, while for parenteral administration physiological saline, an aqueous solution, or an isotonic solution of the desired acid addition salt may be employed. Jellies may also be used for topical administration and may be prepared by incorporating an acid addition salt of 2-amino-4-methylhexane in water, glycerin, and some viscous medium or thickening agent, such as gum tragacanth, sodium alginate or methyl cellulose.

In addition, the 2-amino-4-methylhexane or the acid addition salt of 2-amino-4-methylhexane may be combined with local anesthetic bases. Preferably, an acid addition salt of 2-amino-4-methylhexane is employed with an acid addition salt of the local anesthetic base or the local anesthetic base itself. Such combinations may be used in any suitable form, such as solutions, jellies, or ointments. An especially useful combination is that obtained by incorporating the acid addition salt of 2-amino-4-methylhexane with the acid addition salt of a local anesthetic base in an aqueous solution.

Examples of local anesthetic bases as such or as their acid addition salts for the purposes of this invention are:

Cocaine—methylbenzoylecgonine
Procaine—p-aminobenzoyldiethylaminoethanol
4-(2-methyl-piperidinol-propyl benzoate
p-Amino-benzoyl-dimethylamino-methylbutanol
p-Aminobenzoyl-4-di-n-butylaminopropanol
p-Aminobenzoyl-2-2-dimethyl-3-diethylaminopropanol
Monoisobutylaminoethyl-p-aminobenzoate
Piperidinopropanediol-di-phenylurethane
2-butyloxyquinolinecarboxylic acid-4-diethylethylene-diamine
1-diethylaminopropyl cinnamate

The compositions of this invention are prepared by any one of the following methods:

1. One molecular equivalent of 4-methylhexanone-2 is reacted with slightly more than one molecular equivalent of hydroxylamine. Preferably, the hydroxylamine is prepared in the free

ence of the 4-methylhexanone-2 by reacting the hydrochloride or sulfate or other salt of the hydroxylamine with a suitable base, such as sodium carbonate or sodium hydroxide. Desirably, the reaction mixture is agitated for a few hours to insure the conversion of the 4-methylhexanone-2 to 4-methylhexanone-2 oxime. The resulting 4-methylhexanone-2 oxime separates and is dried by any suitable means, such as with a dehydrating agent, for example, sodium sulfate or magnesium sulfate. After drying, 4-methylhexanone-2 oxime is reduced with hydrogen by means of a catalyst, such as Raney nickel, or by reaction of sodium and a primary alcohol, such as ethanol. The resulting 2-amino-4-methylhexane may be purified by distillation.

2. Another method of preparing the 2-amino-4-methylhexane of this invention is to react one molecular equivalent of 4-methylhexanone-2 with approximately four molecular equivalents of formamide or ammonium formate. The mixture is heated to a temperature of 125°-190° C. and maintained at that temperature until the liberation of ammonium carbonate ceases. This condition may be readily ascertained by observing a condenser attached to the reaction mixture. The reaction product is separated from the excess formamide by adding water to the mixture, agitating, and separating the reaction product, which is insoluble in water, from the water solution. The reaction product is then refluxed with an excess of mineral acid, such as concentrated hydrochloric or dilute sulfuric acid. Desirably, the reaction product is refluxed for a period of from one to two hours, during which time the acid addition salt of 2-amino-4-methylhexane is formed. If the base 2-amino-4-methylhexane is desired, the acid addition salt is treated with a suitable base, such as sodium carbonate or sodium hydroxide. If purification is desired, it may be distilled.

3. A third method of preparing compositions of this invention is to subject a quantity of 4-methylhexanone-2 to the action of ammonia and hydrogen in the presence of a suitable catalyst, such as Raney nickel. Desirably, an excess of ammonia and hydrogen is used and the reaction may be conveniently performed in a bomb by dissolving the ammonia in a solvent, such as ethanol.

If acid addition salts of the base, 2-amino-4-methylhexane, are desired, the 2-amino-4-methylhexane is reacted with an equivalent of the desired acid. The reaction is almost immediate and can be carried out in a suitable solvent, such as ethyl ether, ethanol, or water. In this manner the acid addition salts of 2-amino-4-methylhexane may be formed, such as the acetic, hydrobromic, hydrochloric, sulfuric, maleic, propionic, or malonic acid salts of 2-amino-4-methylhexane.

In the preparation of the 2-amino-4-methylhexane or the acid addition salts of 2-amino-4-methylhexane by the methods outlined herein, racemic mixtures of the *d* and *l* forms of 2-amino-4-methylhexane or the acid addition salts of 2-amino-4-methylhexane result. These racemic mixtures may be removed, if desired, by any of the well-known methods and, after resolution, the *d* or the *l* form may be used alone as a vasoconstrictor or for other purposes instead of the racemic mixtures.

Typical examples of the compositions of this invention and the methods of preparing them are as follows:

Example 1.—Preparation of 2-amino-4-methylhexane.

In a 3-liter flask equipped with a stirrer and thermometer is placed 55 g. (0.83 mol) of hydroxylamine hydrochloride and 175 cc. of cold water. This mixture is stirred until solution is complete. To this solution is added 115 g. (1 mol) of 4-methylhexanone-2. The mixture is stirred and a solution of 80 g. (0.5 mol) of anhydrous sodium carbonate in about 150 cc. of water is added through a dropping funnel. This addition is regulated so that the temperature does not rise above 35° C. During this time 4-methylhexanone-2 oxime is formed. The stirring is continued for 1 to 2 hours after the addition is completed. The mixture separates into two layers, a water layer and a water-insoluble layer. The water-insoluble layer, which contains the 4-methylhexanone-2 oxime, is washed with water and dried with magnesium sulfate or sodium sulfate.

A solution of 80 g. of crude dry 4-methylhexanone-2 oxime in 1800 cc. of absolute ethanol is heated to boiling in a 5-liter flask equipped with an efficient reflux condenser. The source of heat is withdrawn and approximately 200 g. of sodium metal is added as rapidly as possible without essential loss of the ethanol. During this time the 2-amino-4-methylhexane is formed. When all of the sodium is added and reacted, the mixture is cooled and diluted with about 1800 cc. of water. The mixture is distilled through an efficient condenser until no more 2-amino-4-methylhexane comes over. The distillate is adjusted to about pH 6 with hydrochloric acid and the solvents removed by heating in vacuum. The residual material is cooled and made alkaline with strong sodium hydroxide solution. The 2-amino-4-methylhexane is separated from the lower water layer and dried first over solid potassium hydroxide and then over magnesium sulfate. The product, which is 2-amino-4-methylhexane, may be distilled as a colorless liquid, B. P. about 121°-123° C. uncorrected.

Example 2.—Preparation of 2-amino-4-methylhexane.

To a mixture of 20 g. of Raney nickel catalyst and 50 g. of 4-methylhexanone-2 contained in a steel bomb is added 170 cc. of cold absolute ethanol which has been saturated with anhydrous ammonia at −5° C. The resulting mixture is shaken for 3 hours with hydrogen at a pressure of 15 to 150 atmospheres at a temperature of 70° to 100° C. The catalyst is removed by filtration and the filtrate subjected to fractional distillation through an efficient fractionating column. The fraction boiling at about 121°-133° C. consists of 2-amino-4-methylhexane.

Example 3.—Preparation of 2-amino-4-methylhexane.

A mixture of 250 g. (4 mols) of ammonium formate and 115 g. (1 mol) of 4-methylhexanone-2 is heated in a 1-liter flask equipped with a thermometer well and an 8-inch Vigreux column. The top of the Vigreux column is connected to a condenser of large bore set for distillation. The mixture is heated from 150° to 195° C. until distillation stops. The ketone which has distilled over is separated and returned to the reaction flask and the heating continued. Water, carbon dioxide and ammonia are formed as by-products in the reaction. The reaction re-

quires approximately 8 to 10 hours to complete. During this time the formyl derivative of 2-amino-4-methylhexane is formed. When the reaction is completed the mixture is shaken with water and the water-insoluble material separated. The water-insoluble material is refluxed with 150 cc. of concentrated hydrochloric acid for about two hours. During this time the hydrochloride of 2-amino-4-methylhexane is formed. The aqueous solution of the hydrochloride after being freed from any unchanged ketone, as by steam distillation, is cooled and made alkaline with strong sodium hydroxide solution. The separated 2-amino-4-methylhexane is dried first with solid potassium hydroxide and then with anhydrous magnesium sulfate. The 2-amino-4-methylhexane is distilled as a colorless liquid, boiling at about 131°-132° C. uncorrected.

In this preparation formamide may be used instead of ammonium formate with good results. As in the case with ammonium formate best results are obtained by using an excess of formamide.

Example 4.—Preparation of 2-amino-4-methylhexane.

A mixture of 97 g. (0.75 mol) of 4-methylhexanone-2 oxime, 100 cc. of ethanol and 5.0 g. of Raney nickel catalyst is shaken with hydrogen at 15 to 150 atmospheres pressure and a temperature of 75°-100° C. for 5 hours. During this time 2-amino-4-methylhexane is formed. The catalyst is removed by filtration and the filtrate subjected to fractional distillation. The material boiling at about 131°-132° C. uncorrected is collected separately and comprises the desired amine, 2-amino-4-methylhexane.

Example 5.—Preparation of 2-amino-4-methylhexane sulfate.

A mixture of 78 g. of 2-amino-4-methylhexane, 200 cc. of absolute ethanol and 240 cc. of aqueous 2N sulfuric acid is evaporated to dryness on a steam bath. During this time the 2-amino-4-methylhexane sulfate is formed. The white solid is powdered and washed on a Buchner funnel first with ethyl ether-ethanol (1:1) and then with dry ethyl ether. The white solid is dried at 99°-75° C. in an air oven. The product, which is 2-amino-4-methylhexane sulfate, does not have a definite melting point. It is very soluble in water and sparingly soluble in absolute ethanol. It contains a molecule of water of crystallization.

Other acid addition salts of 2-amino-4-methylhexane may be formed by reacting the 2-amino-4-methylhexane with the required acid. For example, 2-amino-4-methylhexane-n-hexyl sulfonate may be produced by reacting 2-amino-4-methylhexane dissolved in a suitable solvent, such as ethyl ether, with a solution of n-hexyl sulfonic acid dissolved in ethyl ether. Likewise, 2-amino-4-methylhexane malate, 2-amino-4-methylhexane benzoate, 2-amino-4-methylhexane glycolate, 2-amino-4-methylhexane nicotinate, 2-amino-4-methylhexane maleate, 2-amino-4-methylhexane gluconate, 2-amino-4-methylhexane phosphate, and 2-amino-4-methylhexane succinate may be prepared by reacting 2-amino-4-methylhexane, dissolved in a suitable solvent, with malic acid, benzoic acid, glycolic acid, nicotinic acid, maleic acid, gluconic acid, phosphoric acid, or succinic acid respectively.

Example 6.—Preparation of 2-amino-4-methylhexane inhalant compound.

An effective 2-amino-4-methylhexane inhalant compound is prepared by incorporating the following in approximately 100 cc. of liquid petrolatum:

2-amino-4-methylhexane	g.	1
Menthol	do	.75
Camphor	do	.75
Oil of thyme	do	.2
Liquid petrolatum to make	do	100

Example 7.—Preparation of 2-amino-4-methylhexane sulfate jelly.

An effective 2-amino-4-methylhexane sulfate jelly is prepared by compounding the following ingredients:

	Grams
2-amino-4-methylhexane sulfate	1
Glycerin	15
Tragacanth	1
Methyl salicylate	.01
Sodium phosphate	.2
Water to make	100

Example 8.—Preparation of 2-amino-4-methylhexane ointment.

An effective ointment of 2-amino-4-methylhexane is compounded from the following ingredients:

	Grams
2-amino-4-methylhexane	1
Menthol	.7
Camphor	.7
Oil of wintergreen	.3
Anhydrous wool fat	8
Liquid petrolatum	25
White petrolatum to make	100

Example 9.—Preparation of solution of acid addition salts of 2-amino-4-methylhexane.

An effective solution of 2-amino-4-methylhexane sulfate for use as a nasal spray is compounded from the following ingredients:

Chlorobutanol	g.	.5
2-amino-4-methylhexane sulfate	do	1
Physiological saline solution	cc.	100

In Examples 7 and 8, acid addition salts of 2-amino-4-methylhexane such as those described in Example 5 may be used instead of 2-amino-4-methylhexane, while in Example 6 oil-soluble acid addition salts such as 2-amino-4-methylhexane oleate may be employed instead of the 2-amino-4-methylhexane. In addition, various other therapeutic compositions may be substituted for the menthol, camphor, methyl salicylate and other ingredients used in the typical Examples 6, 7, and 8. The proportion of all ingredients in these examples may be varied within wide limits, it being understood that these examples are merely typical of a wide variety of solutions, jellies, and ointments which may be prepared with the compositions of this invention.

What is claimed is:

1. A composition selected from the class which consists of 2-amino-4-methylhexane and acid addition salts of 2-amino-4-methylhexane.
2. 2-amino-4-methylhexane.
3. An acid addition salt of 2-amino-4-methylhexane.
4. A solution of a composition selected from the class consisting of 2-amino-4-methylhexane and acid addition salts of 2-amino-4-methylhexane.
5. An isotonic solution of an acid addition salt of 2-amino-4-methylhexane.
6. A 2-amino-4-methylhexane sulfate.

HORACE A. SHONLE
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EXHIBIT 15

The Washington Post

Chemist's New Product Contains Hidden Substance

By Amy Shipley
Washington Post Staff Writer
Monday, May 8, 2006

An Illinois chemist awaiting sentencing for his role in the biggest steroid scandal in U.S. history has for months been involved in marketing a dietary supplement containing a little-known amphetamine-like substance that would be undetectable in current sports drug tests, according to an analysis of the product for The Post.

Patrick Arnold, who in a recent plea deal admitted providing steroids to the drug ring that ensnared Barry Bonds and a number of other famous athletes, runs a company that has been selling the amphetamine-like compound over the Internet in a dietary supplement that describes the substance with the invented trademark name Geranamine.

It is illegal to sell dietary supplements without listing the ingredients by their common or usual names, according to Robert Moore, the Food and Drug Administration's Team Leader in the Division of Dietary Supplement Programs.

The product, Ergopharm's Ergolean AMP, contains an obscure substance that was patented in 1944 and considered for use as an inhalant for nasal decongestion by Eli Lilly and Company. It is known as methylhexaneamine, according to Don Catlin, a noted researcher who analyzed the product and was reimbursed for the work by The Post.

"The chemical structure is similar to amphetamines and ephedrine," said Catlin, whose Los Angeles laboratory provides drug testing for Olympic sports, minor league baseball, the NFL and NCAA. "In this class of drugs, everything depends on the dose. Take enough of it and your heart rate and blood pressure will go up and you can die."

Amphetamines are illegal without a prescription. An official at one of Arnold's companies told The Post the substance was legal because it could be found in nature. Ephedrine, also found in nature, was banned from the dietary supplement market after Baltimore Orioles pitcher Steve Bechler in 2003 died after using it.

Stimulants have been abused by athletes for decades and were considered mainstays in Major League Baseball clubhouses, many players have said publicly, before baseball began a drug testing program in 2004. Because methylhexaneamine would not show up in standard drug screens -- though that will quickly change as soon as Catlin's discovery is publicized -- it could offer athletes in sports that test for stimulants such as ephedrine and amphetamines an alternative that would not produce a positive test.

Athletes have shown they are desperate for such shortcuts. A number of top track and field athletes, including burgeoning superstar Kelli White, were found in 2003 to be using modafinil, which is a

prescription drug used to treat narcolepsy that also is in the amphetamines class. After testing positive for the drug under a strict testing code unique to France, White was forced to relinquish her 2003 world championship medals in the 100 and 200 meters. The drug later was banned by the World Anti-Doping Agency.

Companies that wish to market ingredients that have never before been sold in dietary supplements are required to notify the FDA before doing so and to provide information about the product's safety. The FDA has received no notification about methylhexaneamine from Ergopharm, an FDA spokesperson said. Companies are only exempted from this pre-market notification if the ingredient was marketed in a supplement before 1994 or has a history of use in the food supply.

AMP's label states that the product is a "proprietary blend" of Geranamine, theobroma cacau seed and caffeine. Geranamine has no scientific meaning, Catlin said. The trademark was applied for in January 2005 and is held by Proviant, Ergopharm's parent company. According to the trademark registration, Geranamine is a "constituent of flower oil sold as an integral component of nutritional supplements."

In response to an e-mail query directed to Arnold about methylhexaneamine's presence in AMP and the product's legality, Matthew Daniel, a research and development chemist at Proviant, said Geranamine was found in nature and therefore legal to market in a dietary supplement. He included a reference line to a Chinese research paper.

"Geranamine was found to be in geranium oil that was extracted from geranium plants," Daniel wrote in his only e-mail response. "It is a naturally occuring [sic] compound."

So is ephedrine. Though it is legal to sell naturally occurring compounds in dietary supplements and ephedrine is found in plants, the FDA determined in 2001 that ephedrine produced synthetically could not be considered a legal dietary ingredient.

Daniel and Arnold did not respond to questions as to why methylhexaneamine was not specifically mentioned on the label. They also did not respond to a query about whether they notified the FDA before marketing the product or whether the methylhexaneamine was produced synthetically. The Post sent several e-mails to and left telephone messages with both.

Arnold's sales of the product provide further evidence of the difficulty of lawmakers' and sports officials' attempts to crack down on performance-enhancing drugs in sports. It also highlights the grave problems plaguing the dietary supplement industry since a 1994 act that was intended to make herbal remedies and vitamin products more readily available left the industry virtually unregulated.

The Post reported last fall that six designer steroids were being sold in dietary supplements. Several of the manufacturers discontinued the products, and the FDA issued several warning letters. The FDA oversees the industry, but it does not examine products before they go to market unless companies submit requests to market new dietary ingredients.

Methylhexaneamine is reminiscent of the first steroid Arnold admitted designing for the Bay Area Laboratory Co-Operative (Balco), which federal authorities said provided performance-enhancing drugs to professional athletes in football, baseball and track and field. That steroid, known as norbolethone, also had been the subject of decades-old research, but when the research was abandoned, the substance effectively was forgotten. Because of its obscurity, it wasn't specifically banned when steroids were outlawed in the United States in 1990. Before the 2000 Summer Games in Sydney, Arnold resurrected it and distributed it secretly to athletes. Once federal authorities became aware of it, it was made illegal.

Arnold claims on the Ergopharm Web site that AMP gives dieters and athletes an alternative to ephedrine with fewer negative side effects. AMP has "adrenaline properties" and is "the most powerful weight tool you can purchase without a prescription," Arnold says on the site.

Ergopharm is a division of Proviant Technologies Inc., in Champaign, Ill., which manufactures bulk nutraceutical ingredients and provides contract manufacturing services, according to Ergopharm's Web site. Arnold, the founder of Ergopharm, is a vice president at Proviant. When reached by phone, Proviant's owner, Ramlakhan Boodram, declined an interview request.

The Post obtained a copy of the paper Dainkerian referred to in the company's claim that Geranamine was a natural substance. The paper, which came from an engineering institute in Guiyang, China, claims that there are more than 40 constituents of geranium oil, and that methylhexaneamine is one of them, making up less than 1 percent of the substance (0.66 percent).

Besides the Chinese research paper, The Post could find no other modern research on methylhexaneamine. It was studied in the 1940s and 1950s. Catlin could not find any research indicating oral administration in humans. It is unclear whether the substance is toxic, addictive or has other harmful side effects. The 1944 patent states that methylhexaneamine has fewer side effects than amphetamines and ephedrine, but the FDA has not evaluated it.

"This stuff ought not be out there," Catlin said. "It's dangerous material."

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EXHIBIT 16

newhope 360 from supply to shelf

Jack3d and other MHA-containing supplements fuel adulteration, safety concerns

Tue, 2011-03-15 12:53
Carlotta Mast
Byline: Carlotta Mast

Nutrition Business Journal is calling it the next potential "nightmare" in dietary supplements. Frank Jaksch, CEO of the analytical testing lab ChromaDex, refers to it as "one scary beast." Ed Wyszumiala, general manager of dietary supplement programs at NSF International, says it has him worried about consumer safety. It is methylhexaneamine (MHA), a compound developed by Eli Lilly more than 50 years ago as a nasal decongestant drug. Today, MHA is showing up in a growing number of pre-workout sports nutrition supplements and being labeled as a constituent of geranium oil. The ingredient was a popular topic of discussion during last week's Nutracon and Natural Products Expo West/SupplyExpo.

Why the concern?

For Wyszumiala, one problem lies in the fact that extensive NSF analysis has shown that geranium oil—which is an approved food flavoring that is legal for use in dietary supplements—does not contain MHA. "This is not a supplement ingredient," Wyszumiala told NewHope360.com. Manufacturers using MHA in their sports nutrition products say otherwise, but their main piece of evidence is one questionable study published by Guizhou University in China.

Wyszumiala said his team had the study translated from Chinese to English and does not put any credence in the research. According to *NBJ*, which investigated MHA/geranium oil topic in its February 2011 Sports Nutrition & Weight Loss issue, the Chinese paper contains "a possible typo" — hexanamide is referenced, not hexanamine—that "calls the entire relevancy of the data into question."

MHA: Dangerous at high dosages

Aside from being a potential dietary supplement

adulterant, MHA is also fueling worry because of its powerful stimulating effects. In a 2006 *Washington Post* article on the synthetic ingredient, Don Catlin, MD, CEO of the Anti-Doping Research Group, said the chemical structure of MHA is akin to amphetamines and ephedrine. "In this class of drugs, everything depends on the dose," Catlin said. "Take enough of it and your heart rate and blood pressure will go up and you can die."

And herein lies a serious problem, Wyszumiala said. MHA is a key ingredient in one of the most popular pre-workout sports supplements: USP Labs' Jack3d—a product that can be found in high school locker rooms and weight rooms throughout the country. "Jack3d is very popular with high school students," Wyszumiala said. "I worry about those young athletes who decide to take more than the recommended dose. It could be very dangerous for them."

In its marketing for Jack3d, USP Labs touts the product's ability to "give you the mad aggressive desire and ability to lift more weight." In online testimonials for the product—of which there are many—many users echo this sentiment ("I had the best workout I've had in months," wrote one), while also noting Jack3d's stimulating effects. "I took it the other day and had to make a stop at a business on the way to the gym. I felt like a crackhead talking to this lady who worked there ... I was tingling all over and trying not to giggle or twitch like a tweaker."

MHA was banned by the World Anti-Doping Agency in 2010. Jack3d is on the list of products banned by the NCAA. MHA and geranium oil extract can be found in numerous other products including E-Pharm's ClearShot, an energy drink concocted by Patrick Arnold, the steroid designer behind the BALCO scandal. "We see it appearing more and more frequently, especially in the energy beverage category," Jaksch told *NBJ*.

Industry gives MHA a closer look

In its reporting on MHA, *Nutrition Business Journal* contacted the U.S. Food and Drug Administration (FDA) for comment. The agency's response: "FDA is aware of the ingredient but we do not have any direct evidence that would lead us to conclude that it is unsafe."

Although the FDA is not yet moving on treating MHA as a supplement adulterant, Wyszumiala said the U.S. supplement trade associations are paying closer attention to the ingredient and its use. This, Wyszumiala added, is encouraging. "We have an opportunity here to deal with what could be another serious adulteration issue in dietary supplements," he said.

Many conversations during last week's Nutracon ingredients conference focused on the potential dangers surrounding MHA and geranium oil extract. During the event, Anthony Almada, a biochemist and president and CEO of GENr8, told Nutraingredients-USA.com that discussions on this topic once held behind "closed doors" are now finally going public.

Almada also said that he believes the concern surrounding this popular sports nutrition ingredient will escalate. "I expect there to be a mushroom cloud sighting before summer."

ChromaDex's Jaksch told *NBJ* that he feels the "geranium story will end badly" for the dietary supplement industry if it doesn't take appropriate action. "It's a scary beast," he said. "The industry just doesn't need another story like that."

Source URL: http://newhope360.com/sports-and-fitness-performance/jack3d-and-other-mha-containing-supplements-fuel-adulteration-safety-

EXHIBIT 17

New pill ingredient worries ministry

Published: 10:13AM Saturday October 04, 2008 Source: ONE News/Newstalk ZB

A new party pill ingredient is worrying the Ministry of Health enough to call for retailers to stop selling it in its pure form.

BZP may be off the shelves now, but an ingredient they are calling Geranium Oil Extract or DMAA has left some users sick.

Six months after the party pill BZP was banned, unlike the last time, this incident is making the industry sing the same tune.

Matt Bowden, of Social Tonics Association, said they share the ministry's concerns.

"DMAA should not be sold in gram bags of powder, overdose bags. It's not a good look," says Bowden.

The Health Ministry is trying to stop the sale of bags of white powder Di-methyl-amyl-amine or DMAA, after four users ended up sick in Waikato hospital.

Many retailers do not stock pure DMAA powder, saying they do not trust it as they are not sure about the manufacturers.

But people seeking the drug only need to go online and there are two websites where anyone over the age of 18 can buy it, no questions asked.

The powder is even being sold on the sites in five gram containers, which is hundreds of time the recommended dose.

The Drug Foundation's Ross Bell says it was a similar situation when BZP first hit the market, being sold in unmarked containers and quite high level of dosages.

There are party pills that use DMAA as an ingredient, although the party pill industry says in that form, there is nothing to worry about.

"It's only if you take large concentrated amount in a bag and start selling it, that's when you start having trouble," says Bowden.

DMAA's sometimes labelled as Geranium Oil Extract, but some warn that Natural doesn't mean harmless.

"If you believe the industry, it sounds like there's pixies dancing in the field picking natural ingredients and making these wonderf safe products and we know that's not the case," says Bell.

The Drug Foundation is suggesting party pill users seek out better information about what they're taking, whatever that is.

At the moment, the government cannot force people who have DMAA to hand it over, because it doesn't come under the Misuse Drugs Act.

The question of DMAA's continued legality will be up for review next month.

Meanwhile, an Otago University study has backed concerns that the initial BZP party pill ban would simply boost the illegal drug market.

Surveys of students found one in six were more likely to take ecstasy as a replacement now that the legal alternative was no long legal.

However, two thirds of students surveyed said they would no longer use BZP party pills now they were illegal.

EXHIBIT 18

WORLD ANTI-DOPING AGENCY

The World Anti-Doping Code

THE 2011 PROHIBITED LIST

INTERNATIONAL STANDARD

The official text of the *Prohibited List* shall be maintained by *WADA* and shall be published in English and French. In the event of any conflict between the English and French versions, the English version shall prevail.

This List shall come into effect on 1 January 2011

The 2011 Prohibited List
18 September 2010

THE 2011 PROHIBITED LIST
WORLD ANTI-DOPING CODE

Valid 1 January 2011

All *Prohibited Substances* shall be considered as "Specified Substances" except Substances in classes S1, S2.1 to S2.5, S.4.4 and S6.a, and *Prohibited Methods* M1, M2 and M3.

SUBSTANCES AND METHODS PROHIBITED AT ALL TIMES (IN- AND OUT-OF-COMPETITION)

S0. NON-APPROVED SUBSTANCES

Any pharmacological substance which is not addressed by any of the subsequent sections of the List and with no current approval by any governmental regulatory health authority for human therapeutic use (i.e. drugs under pre-clinical or clinical development or discontinued) is prohibited at all times.

PROHIBITED SUBSTANCES

S1. ANABOLIC AGENTS

Anabolic agents are prohibited.

1. Anabolic Androgenic Steroids (AAS)

a. Exogenous* AAS, including:

1-androstenediol (5α-androst-1-ene-3β,17β-diol); **1-androstenedione** (5α-androst-1-ene-3,17-dione); **bolandiol** (19-norandrostenediol); **bolasterone; boldenone; boldione** (androsta-1,4-diene-3,17-dione); **calusterone; clostebol; danazol** (17α-ethynyl-17β-hydroxyandrost-4-eno[2,3-d]isoxazole); **dehydrochlormethyltestosterone** (4-chloro-17β-hydroxy-17α-methylandrosta-1,4-dien-3-one); **desoxymethyltestosterone** (17α-methyl-5α-androst-2-en-17β-ol); **drostanolone; ethylestrenol** (19-nor-17α-pregn-4-en-17-ol); **fluoxymesterone; formebolone; furazabol** (17β-hydroxy-17α-methyl-5α-

androstano[2,3-c]-furazan); **gestrinone; 4-hydroxytestosterone** (4,17β-dihydroxyandrost-4-en-3-one); **mestanolone; mesterolone; metenolone; methandienone** (17β-hydroxy-17α-methylandrosta-1,4-dien-3-one); **methandriol; methasterone** (2α, 17α-dimethyl-5α-androstane-3-one-17β-ol); **methyldienolone** (17β-hydroxy-17α-methylestra-4,9-dien-3-one); **methyl-1-testosterone** (17β-hydroxy-17α-methyl-5α-androst-1-en-3-one); **methylnortestosterone** (17β-hydroxy-17α-methylestr-4-en-3-one); **methyltestosterone; metribolone** (methyltrienolone, 17β-hydroxy-17α-methylestra-4,9,11-trien-3-one); **mibolerone; nandrolone; 19-norandrostenedione** (estr-4-ene-3,17-dione); **norboletone; norclostebol; norethandrolone; oxabolone; oxandrolone; oxymesterone; oxymetholone; prostanozol** (17β-hydroxy-5α-androstano[3,2-c] pyrazole); **quinbolone; stanozolol; stenbolone; 1-testosterone** (17β-hydroxy-5α-androst-1-en-3-one); **tetrahydrogestrinone** (18a-homo-pregna-4,9,11-trien-17β-ol-3-one); **trenbolone;** and other substances with a similar chemical structure or similar biological effect(s).

b. Endogenous** AAS when administered exogenously:

androstenediol (androst-5-ene-3β,17β-diol); **androstenedione** (androst-4-ene-3,17-dione); **dihydrotestosterone** (17β-hydroxy-5α-androstan-3-one); **prasterone** (dehydroepiandrosterone, DHEA); **testosterone**
and the following metabolites and isomers:

5α-androstane-3α,17α-diol; 5α-androstane-3α,17β-diol; 5α-androstane-3β,17α-diol; 5α-androstane-3β,17β-diol; androst-4-ene-3α,17α-diol; androst-4-ene-3α,17β-diol; androst-4-ene-3β,17α-diol; androst-5-ene-3α,17α-diol; androst-5-ene-3α,17β-diol; androst-5-ene-3β,17α-diol; 4-androstenediol (androst-4-ene-3β,17β-diol); **5-androstenedione** (androst-5-ene-3,17-dione); **epi-dihydrotestosterone; epitestosterone; 3α-hydroxy-5α-androstan-17-one; 3β-hydroxy-5α-androstan-17-one; 19-norandrosterone; 19-noretiocholanolone.**

2. Other Anabolic Agents, including but not limited to:

Clenbuterol, selective androgen receptor modulators (SARMs), tibolone, zeranol, zilpaterol.

For purposes of this section:
* *"exogenous" refers to a substance which is not ordinarily capable of being produced by the body naturally.*
** *"endogenous" refers to a substance which is capable of being produced by the body naturally.*

S2. PEPTIDE HORMONES, GROWTH FACTORS AND RELATED SUBSTANCES

The following substances and their releasing factors are prohibited:

1. **Erythropoiesis-Stimulating Agents** [e.g. **erythropoietin (EPO), darbepoetin (dEPO), hypoxia-inducible factor (HIF) stabilizers, methoxy polyethylene glycol-epoetin beta (CERA), peginesatide (Hematide)];**

2. **Chorionic Gonadotrophin (CG) and Luteinizing Hormone (LH)** in males;

3. **Insulins;**

4. **Corticotrophins;**

5. **Growth Hormone (GH), Insulin-like Growth Factor-1 (IGF-1), Fibroblast Growth Factors (FGFs), Hepatocyte Growth Factor (HGF), Mechano Growth Factors (MGFs), Platelet-Derived Growth Factor (PDGF), Vascular-Endothelial Growth Factor (VEGF)** as well as any other growth factor affecting muscle, tendon or ligament protein synthesis/degradation, vascularisation, energy utilization, regenerative capacity or fibre type switching;

and other substances with similar chemical structure or similar biological effect(s).

S3. BETA-2 AGONISTS

All beta-2 agonists (including both optical isomers where relevant) are prohibited except salbutamol (maximum 1600 micrograms over 24 hours) and salmeterol when taken by inhalation in accordance with the manufacturers' recommended therapeutic regime.

The presence of salbutamol in urine in excess of 1000 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an *Adverse Analytical Finding* unless the *Athlete* proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of a therapeutic dose (maximum 1600 micrograms over 24 hours) of inhaled salbutamol.

S4. HORMONE ANTAGONISTS AND MODULATORS

The following classes are prohibited:

1. **Aromatase inhibitors** including, but not limited to: **aminoglutethimide, anastrozole, androsta-1,4,6-triene-3,17-dione (androstatrienedione), 4-androstene-3,6,17 trione (6-oxo), exemestane, formestane, letrozole, testolactone.**

2. **Selective estrogen receptor modulators (SERMs)** including, but not limited to: **raloxifene, tamoxifen, toremifene.**

3. **Other anti-estrogenic substances** including, but not limited to: **clomiphene, cyclofenil, fulvestrant.**

4. **Agents modifying myostatin function(s)** including, but not limited, to: **myostatin inhibitors.**

S5. DIURETICS AND OTHER MASKING AGENTS

Masking agents are prohibited. They include:
Diuretics, desmopressin, plasma expanders (e.g. **glycerol**; intravenous administration of **albumin, dextran, hydroxyethyl starch** and **mannitol), probenecid;** and other substances with similar biological effect(s).

Diuretics include:
Acetazolamide, amiloride, bumetanide, canrenone, chlorthalidone, etacrynic acid, furosemide, indapamide, metolazone, spironolactone, thiazides (e.g. **bendroflumethiazide, chlorothiazide, hydrochlorothiazide), triamterene**; and other substances with a similar chemical structure or similar biological effect(s) (except drosperinone, pamabrom and topical dorzolamide and brinzolamide, which are not prohibited).

The use *In-* and *Out-of-Competition,* as applicable, of any quantity of a substance subject to threshold limits (i.e. salbutamol, morphine, cathine, ephedrine, methylephedrine and pseudoephedrine) in conjunction with a diuretic or other masking agent requires the deliverance of a specific Therapeutic Use Exemption for that substance in addition to the one granted for the diuretic or other masking agent.

PROHIBITED METHODS

M1. ENHANCEMENT OF OXYGEN TRANSFER

The following are prohibited:

1. Blood doping, including the use of autologous, homologous or heterologous blood or red blood cell products of any origin.

2. Artificially enhancing the uptake, transport or delivery of oxygen, including, but not limited to, perfluorochemicals, efaproxiral (RSR13) and modified haemoglobin products (e.g. haemoglobin-based blood substitutes, microencapsulated haemoglobin products), excluding supplemental oxygen.

M2. CHEMICAL AND PHYSICAL MANIPULATION

The following is prohibited:

1. *Tampering,* or attempting to tamper, in order to alter the integrity and validity of *Samples* collected during *Doping Control* is prohibited. These include but are not limited to catheterisation, urine substitution and/or adulteration (e.g. proteases).

2. Intravenous infusions are prohibited except for those legitimately received in the course of hospital admissions or clinical investigations.

3. Sequential withdrawal, manipulation and reinfusion of whole blood into the circulatory system is prohibited.

M3. GENE DOPING

The following, with the potential to enhance sport performance, are prohibited:

1. The transfer of nucleic acids or nucleic acid sequences;

2. The use of normal or genetically modified cells;

3. The use of agents that directly or indirectly affect functions known to influence performance by altering gene expression. For example, Peroxisome Proliferator Activated Receptor δ (PPARδ) agonists (e.g. GW 1516) and PPARδ-AMP-activated protein kinase (AMPK) axis agonists (e.g. AICAR) are prohibited.

SUBSTANCES AND METHODS PROHIBITED IN-COMPETITION

In addition to the categories S0 to S5 and M1 to M3 defined above, the following categories are prohibited *In-Competition*:

PROHIBITED SUBSTANCES

S6. STIMULANTS

All stimulants (including both optical isomers where relevant) are prohibited, except imidazole derivatives for topical use and those stimulants included in the 2011 Monitoring Program*.

Stimulants include:

a: Non-Specified Stimulants:

Adrafinil; amfepramone; amiphenazole; amphetamine; amphetaminil; benfluorex; benzphetamine; benzylpiperazine; bromantan; clobenzorex; cocaine; cropropamide; crotetamide; dimethylamphetamine; etilamphetamine; famprofazone; fencamine; fenetylline; fenfluramine; fenproporex; furfenorex; mefenorex; mephentermine; mesocarb; methamphetamine(*d*-); p-methylamphetamine; methylenedioxyamphetamine; methylenedioxymethamphetamine; modafinil; norfenfluramine; phendimetrazine; phenmetrazine; phentermine; 4-phenylpiracetam (carphedon); prenylamine; prolintane.
A stimulant not expressly listed in this section is a Specified Substance.

b: Specified Stimulants (examples):

Adrenaline; cathine***; ephedrine****; etamivan; etilefrine; fenbutrazate; fencamfamin; heptaminol; isometheptene; levmetamfetamine; meclofenoxate; methylephedrine****; methylhexaneamine (dimethylpentylamine); methylphenidate; nikethamide; norfenefrine; octopamine; oxilofrine; parahydroxyamphetamine; pemoline; pentetrazol; phenpromethamine; propylhexedrine; pseudoephedrine*****; selegiline; sibutramine; strychnine; tuaminoheptane;** and other substances with a similar chemical structure or similar biological effect(s).

* The following substances included in the 2011 Monitoring Program (bupropion, caffeine, phenylephrine, phenylpropanolamine, pipradol, synephrine) are not considered as *Prohibited Substances*.
** **Adrenaline** associated with local anaesthetic agents or by local administration (e.g. nasal, ophthalmologic) is not prohibited.
*** **Cathine** is prohibited when its concentration in urine is greater than 5 micrograms per milliliter.
**** Each of **ephedrine** and **methylephedrine** is prohibited when its concentration in urine is greater than 10 micrograms per milliliter.
***** **Pseudoephedrine** is prohibited when its concentration in urine is greater than 150 micrograms per milliliter.

S7. NARCOTICS

The following are prohibited:

Buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, pethidine.

S8. CANNABINOIDS

Natural (e.g. cannabis, hashish, marijuana) or synthetic delta 9-tetrahydrocannabinol (THC) and cannabimimetics [e.g. "Spice" (containing JWH018, JWH073), HU-210] are prohibited.

S9. GLUCOCORTICOSTEROIDS

All glucocorticosteroids are prohibited when administered by oral, intravenous, intramuscular or rectal routes.

EXHIBIT 19

Army probing connection between body building supplement, 2 deaths

By TRAVIS J. TRITTEN
Stars and Stripes
Published: December 15, 2011

CAMP FOSTER, Okinawa – The U.S. Army said it is investigating whether a popular bodybuilding and weight-loss supplement might be to blame for two soldier deaths and serious health problems in others, including liver and kidney damage.

The two soldiers suffered heart attacks and died earlier this year during physical training with their units at an Army base in the southwestern United States and the dietary supplement DMAA was discovered in their bodies following toxicology tests, according to Army spokeswoman Maria Tolleson.

The Army launched an ongoing safety review after recording a number of other serious health effects among known and potential users of products containing DMAA including "kidney and liver failure, seizures, loss of consciousness, heat injury and muscle breakdown during exertion, and rapid heartbeat," Tolleson said in a written response to Stars and Stripes this week.

Bodybuilding and weight-loss pills and powders containing DMAA, which is widely marketed by the fitness supplement industry as geranium extract and 1,3 dimethylamylamine, were pulled from shelves at Army and Air Force Exchange Service and Navy Exchange stores around the world following a military product recall Dec. 3.

Retailer GNC and at least one maker of the products said Friday that products containing DMAA have been tested as safe and have not been linked to any other health problems.

"There is no scientific or medical evidence that demonstrates any causal link between DMAA and any adverse medical condition, let alone a death," according to GNC spokesman Greg Miller.

All of the recalled DMAA products are supplied to GNC and its stores within military exchanges by third-party manufacturers, which have shown the retailer they are safe, Miller wrote in an email response to Stars and Stripes.

"Compared to the handful of adverse event reports recently cited by the Army, GNC has sold 440 million doses of product containing DMAA since 2007 and has not received a single serious adverse event report," according to Miller.

DMAA is now considered a dietary supplement by the U.S. Food and Drug Administration, a category of product that does not require FDA review before it is sold.

"A firm does not have to provide FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products," according to the federal agency.

USPlabs, the manufacturer of the recalled supplements Jack3d and OxyElite Pro, said testing has shown its products could not be responsible for the health problems reported by the Army.

"Published, peer-reviewed clinical data says no. There are no facts that state otherwise," USPlabs spokesman Jack Deschauer said. "Our products have undergone intense scientific, clinical studies for safety and efficacy by experts in the field of sports nutrition and there is no evidence the products could cause such injuries."

The company pointed to four studies just published in a peer-reviewed medical journal that showed DMAA products did not seem cause any negative effects to the blood, blood pressure or heart rate when taken by test subjects for a short period.

"We are confident that once the [Army] review is complete, the safety of our products will be confirmed," Deschauer said.

The Army did not immediately say how long its safety review of DMAA could last.

The Army surgeon general has asked the Health Policy and Services Directorate and Army Public Health Command to review and validate the science regarding the supplement's safety, according to Tolleson.

The military has recently warned that servicemembers could be at an increased risk of heart problems due to extreme physical exertion, especially downrange in mountainous Afghanistan.

The widespread use of fitness supplements such as DMAA that stimulate the metabolism and nervous system could increase the dangers of heart palpitations, dizziness and other heart conditions, physicians at Landstuhl Regional Medical Center in Germany and Brooke Army Medical Center in Texas said in January.

The first death with a potential link to DMAA occurred over the summer, the service said.

A 22-year-old soldier collapsed and died during a PT run with his unit. Then in the fall, a 32-year-old soldier collapsed at the same base after taking the Army physical fitness test and died after being hospitalized for one month, Tolleson said. The Army did not name the base where the soldiers were stationed.

“Both soldiers were performing PT with their units when they experienced cardiac arrest,” she said.

trittent@pstripes.osd.mil

Supplements

Body building supplements are basically drugs. But they are not illicit or illegal at all. They are proven safe. However, taking too much will surely have adverse effects if not fatal. It's just like other drugs which if overdosed, can cause side effects if not death.

Like
Reply
2 months ago

spajarillo

I have taken Oxy before and been fine...EXERCISE CAREFULLY, DRINK PLENTY OF WATER, EAT HEALTHIER, AND DO NOT OD...
Im not skinny, nor am I "fit" but then again I have had 3 kids, and twins at that! I seriously believe they took more than what is suggested on the label! I may be wrong, but then again...*shrugs* who knows!

Like
Reply
3 months ago

Bodybuilding Supplements

Oh come now, we all know why noone has drawn attention to this power drink and weight-loss fitness supplement problem. AAFES makes a lot of money and the "private sectors" ability to profit can't be compromised.

Like
Reply
4 months ago

Jerome Joshua Lopez

They weren't in poor health. They both took 3 times the recommended dosage and weren't drinking nearly enough water. Mix those two together during morning PT and you get cardiac arrest...

Like

Reply
5 months ago
in reply to Karly Woodle

buy steroids uk

imho many supps are more dangerous than steroids.

Like
Reply
5 months ago

Karly Woodle

Why is it that when unfortunate incidents such as these happen, people look to place the blame on someone/something other than the person themselves. It was mentioned above that the Army doesn't encourage proper diet, so who is to know if the people affected were already in poor health before taking Oxyelite? Just like anything else in life, don't overuse/abuse anything or expect any sort of product to be a miracle

Like
Reply
6 months ago

SOCOMM

Going_Home

Well Played Sir.

My 2 cents - Monster, Rock Star, AAFES Jolt High Caffeine Coffee, Starbucks Doubleshot Espresso are, in my opinion, more widely abused then the performance enhancers.
What about providing soldiers water? Oh thats right, I can go buy it at AAFES.

Like
Reply
6 months ago
in reply to SOCOMM

Going_Home

The Army pushes for fitness and does not provide a proper diet. To get the energy boost it takes to work Army Standard required hours, it is easy to go for the go juice or some other performance booster.

Body building supplements are performance boosters and service members want to be the best. Providing GNC's in the bases exchanges provides access to all the supplements once could need as well as all the energy drinks that can be stocked. There is a military culture that has become socially excepted to push the soldiers until they can't do no more. The use of supplements is supposed to enhance the performance of the soldiers. As noted above the cause of kidney problems deployed by service members is associated with consumption of sports drinks. The same sports drinks that claim to enhance energy. But as person in immediate danger at all times wouldn't you want to have extra energy too?

As we can see by the unfortunate deaths linked to body building supplements this displays a failure of education and understanding by the exchange and DeCA, where the products are available.

Please someone from DeCA or the exchange explain how a service member who is perpetually in a high stress situation, who does not always have access to potable water, who has not slept properly for an extended period of time, and who has been in an elevated state of alertness (acute stress response) from the day they signed the dotted line is the same as the person that takes the supplements in the control test for the performance enhancers. Active duty is not a control test.

Essentially, the exchange is providing a drug that can harm you if taken outside of proper conditions; and the exchange goes where you go ~ in all the improper places we can find.The military has forgot that athletes need proper exercise, proper rest, and proper nutrition to preform at peek performance. Providing enhancement products in absence of caring for the wellbeing of our service members is a continuous problem.

If the exchange wants to supply drugs they should supply THC and amphetamines. THC for the PTSD and amphetamines so we can get a performance boost that is expected by the use of supplements. With THC service members could get some rest, and use that energy along with the amphetamines too end these wars sooner.

I cannot stand by the truth in this article (except for the 2 deaths), but neither can the positive health effects that performance supplements can provide to service members in austere environments or on Active Duty.

Like
Reply
6 months ago
1 Like

A S

Thank you for the information; do most of those energy drinks contain the same extract? I was under the impression that they don't. But thank you for the information about the energy drinks and kidney failure.

Like
Reply
6 months ago
in reply to tiredofpc

WilliamWestmoreland

Oh come now, we all know why noone has drawn attention to this power drink and weight-loss fitness supplement problem. AAFES makes a lot of money and the "private sectors" ability to profit can't be compromised. Certainly not by evil "big government" ask your Republican congressman.

Like
Reply
6 months ago
2 Likes

bassfishnjunkie

It is interesting that after several deaths speculated to be "weight loss pill" related, we still have GNC stores in our PX's. I am sure that many Soldiers take their supplements safely, but why have these stores so readily available when you run the risk of young Soldiers not understanding the effects this stuff can have if taken incorrectly. I can see this becoming part of weekend safety briefings etc. Just more stuff for us to worry about!

Like
Reply
6 months ago
1 Like

wllmshrwn

It says on the label of all of these products that you must consume 1 gallon of water per day. I wonder how much water, if any, these individuals were consuming. I've been taking Jack3d for well over the past year and haven't had any problems. Plus how much did they take in one dose is also to be determined.

Like
Reply
6 months ago
2 Likes

SOCOMM

Why not list the products? Here you go: USPlabs Jack3d (Tropical Fruit and Lemon Lime) USPlabs OxyELITE Pro, Nutrex Research Lipo-6 Black (his and hers), Nutrex Research Lipo-6 Black Ultra Concentrate (his and hers), Nutrex Research Hemo-Rage Black Powder, Punch, Berry, iSatori PWR, Muscletech NeuroCore, Muscletech HydroxyStim,
Fahrenheit Nutrition Lean EFX, Muscle Warfare Napalm, SNI Nitric Blast, BIORhythm SSIN Juice, MuscleMeds Code Red, SEI MethylHex 4,2, Gaspari Nutrition Spirodex

Like
Reply
6 months ago
4 Likes

tiredofpc

While deployed to LRMC, Feb '05 through Dec '06, we saw multiple very young and not so young service members come into LRMC with acute kidney failure. Some of these folks responded to medical treatments and/or dialysis done on the German economy, in German hospitals. Some recovered their kidney function some did not, but all were impacted as to their long term kidney function and survivability. Those of you not familiar with dialysis, it requires the person going to a dialysis center three days a week, spending multiple hours at dialyzing, and then coming back a few days later; an enormous impact on your life, quality of life, and ability to live any kind of "normal" llife.These were previously healthy, young men and women with normal kidney function, who's history was similar in that they'd drank so called "power drinks" one or more times a day. This was early deployment times, spring through fall time frames for those down range in Iraq with really ugly living/serving situations, including ambient temperatures off the charts, wearing all the "battle rattle gear", lots of night time patrols while sleeping in cooled conditions prior to patrol only if you were luck), and required PT sometimes during the daylight,hot hours. These folks came into LRMC in acute kidney failure, requiring dialysis. I don't know why the Army wasn't either doing or publicizing research done then into the link between "power drinks" and acute kidney failure. I'm certainly not surprised to see this information years and years later.

Like
Reply
6 months ago
4 Likes

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Real-time updating is **enabled**. (Pause)

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Comments Policy

EXHIBIT 20

U.S. Department of Health & Human Services

U.S. Food & Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: April 27, 2012
Media Inquiries: Tamara Ward, 301-796-7567, tamara.ward@fda.hhs.gov
Trade Press Inquiries: Sebastian Cianci, 240-402-2291, sebastian.cianci@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA challenges marketing of DMAA products for lack of safety evidence
Agency cites ten companies in warning letters

The U.S. Food and Drug Administration today issued warning letters to ten manufacturers and distributors of dietary supplements containing dimethylamylamine, more popularly known as DMAA, for marketing products for which evidence of the safety of the product had not been submitted to FDA.

Also referred to as 1,3-dimethylamylamine, methylhexanamine, or geranium extract, the ingredient is in dietary supplements and is often touted as a "natural" stimulant.

The companies receiving warning letters and their product names are:

Company	Product(s)
Exclusive Supplements [1]	Biorhythm SSIN Juice
Fahrenheit Nutrition [2]	Lean Efx
Gaspari Nutrition [3]	Spirodex
iSatori Global Technologies, LLC [4]	PWR
Muscle Warfare, Inc. [5]	Napalm
MuscleMeds Performance Technologies [6]	Code Red
Nutrex Research [7]	Hemo Rage Black
	Lipo-6 Black Ultra Concentrate
	Lipo-6 Black
	Lipo-6 Black Hers Ultra Concentrate
	Lipo-6 Black Hers
SEI Pharmaceuticals [8]	MethylHex 4,2
SNI LLC [9]	Nitric Blast
USP Labs, LLC [10]	Oxy Elite Pro
	Jack3D

"Before marketing products containing DMAA, manufacturers and distributors have a responsibility under the law to provide evidence of the safety of their products. They haven't done that and that makes the products adulterated," said Daniel Fabricant, Ph.D., Director of FDA's Dietary Supplement Program.

Specifically, the warning letters cite the companies for marketing products for which a notification had not been submitted for the use of DMAA as a New Dietary Ingredient (NDI). Under current law, dietary supplement manufacturers or distributors who use certain dietary ingredients not marketed in a dietary supplement prior to October 15, 1994, are responsible for notifying the FDA of evidence to support their conclusion that their dietary supplements containing NDIs are safe. Manufacturers or distributors must submit notification at least 75 days before marketing their products. The companies warned today were marketing products for which this requirement had not been met.

The FDA warning letters also advised the companies that the agency is not aware of evidence or history of use to indicate that DMAA is safe. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), manufacturers, marketers and distributors of dietary supplements are responsible for ensuring that they are marketing a safe product.

The FDA letters noted that DMAA is known to narrow the blood vessels and arteries, which can elevate blood pressure and may lead to cardiovascular events ranging from shortness of breath and tightening in the chest to heart attack. The agency has received 42 adverse event reports on products containing DMAA. While the complaints do not establish that DMAA was the cause of the incidents, some of the reports have included cardiac disorders, nervous system disorders, psychiatric disorders, and death.

The agency additionally warned the companies that synthetically-produced DMAA is not a "dietary ingredient" and, therefore, is not eligible to be used as an active ingredient in a dietary supplement. DSHEA defines a dietary ingredient as a vitamin, mineral, amino acid, herb or other botanical, a dietary substance for use by man to supplement the diet, or a concentrate, metabolite, constituent, extract, or combination of these substances.

The companies have 15 business days to respond to the FDA with the specific steps they will take to address the issues in the warning letters.

For more information:

How dietary supplements are regulated [11]

Dietary Supplement Health and Education Act of 1994 [12]

New Dietary Ingredient notification process [13]

Reporting adverse events associated with FDA regulated products[14]

#

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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19. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
20. http://www.youtube.com/user/USFoodandDrugAdmin?blend=23&ob=5
21. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
22. http://twitter.com/us_fda
23. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
24. /AboutFDA/ContactFDA/StayInformed/RSSFeeds/PressReleases/rss.xml

10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

Links on this page:

1. /ICECI/EnforcementActions/WarningLetters/2012/ucm302162.htm
2. /ICECI/EnforcementActions/WarningLetters/2012/ucm302261.htm
3. /ICECI/EnforcementActions/WarningLetters/2012/ucm302211.htm
4. /ICECI/EnforcementActions/WarningLetters/2012/ucm302202.htm
5. /ICECI/EnforcementActions/WarningLetters/2012/ucm302160.htm
6. /ICECI/EnforcementActions/WarningLetters/2012/ucm302279.htm
7. /ICECI/EnforcementActions/WarningLetters/2012/ucm302165.htm
8. /ICECI/EnforcementActions/WarningLetters/2012/ucm302295.htm
9. /ICECI/EnforcementActions/WarningLetters/2012/ucm302078.htm
10. /ICECI/EnforcementActions/WarningLetters/2012/ucm302167.htm
11. /Food/DietarySupplements/default.htm
12. /RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148003.htm
13. /Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/default.htm
14. /Safety/ReportaProblem/ConsumerComplaintCoordinators/default.htm
15. https://blogs.fda.gov/fdavoice/
16. http://www.facebook.com/FDA
17. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
18. http://www.flickr.com/photos/fdaphotos/
19. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
20. http://www.youtube.com/user/USFoodandDrugAdmin?blend=23&ob=5

21. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
22. http://twitter.com/us_fda
23. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm
24. /AboutFDA/ContactFDA/StayInformed/RSSFeeds/PressReleases/rss.xml

EXHIBIT 21

U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Nutrex Research, Inc. 4/24/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

April 24, 2012

WARNING LETTER

VIA OVERNIGHT DELIVERY

Nutrex Research, Inc.
5707 Dot Com Ct. #1001
Ovideo, FL 32765

Dear Sir or Madam:

This letter concerns your products Hemo Rage Black, Lipo-6 Black Ultra Concentrate, Lipo-6 Black, Lipo-6 Black Hers Ultra Concentrate, and Lipo-6 Black Hers, which are labeled and/or promoted as dietary supplements. The product labeling for Hemo Rage Black, Lipo-6 Black, and Lipo-6 Black Hers declares 1,3- dimethylamylamine HCl as a dietary ingredient, and the product labeling for Lipo-6 Black Ultra Concentrate and Lipo-6 Black Hers Ultra Concentrate declares methylhexaneamine as a dietary ingredient. These two names refer to the same ingredient, which is also called, among other names, dimethylamylamine, DMAA or methylhexanamine, and will be referred to in the rest of this letter as dimethylamylamine.

The term "dietary supplement" is defined in 21 U.S.C. 321(ff) [section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the Act)]. Given that you have declared dimethylamylamine as a dietary ingredient in the labeling of your products, we assume you have a basis to conclude that dimethylamylamine is a “dietary ingredient” under 21 U.S.C. 321(ff)(1). Assuming that dimethylamylamine is a "dietary ingredient," it would also be a “new dietary ingredient” for which a notification is required under 21 U.S.C. 350b(a)(2) and 21 CFR 190.6.

Under 21 U.S.C. 350b, a dietary supplement that contains a new dietary ingredient (i.e., a dietary ingredient not marketed in the United States before October 15, 1994) shall be deemed adulterated under 21 U.S.C. 342(f) unless it meets one of two requirements:

1. The dietary supplement contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or

2. There is a history of use or other 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 and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

To the best of FDA’s knowledge, there is no information demonstrating that dimethylamylamine was lawfully marketed as a dietary ingredient in the United States before October 15, 1994, nor is there information demonstrating that this ingredient has been present in the food supply as an article used for food in a form in which the food has not been chemically altered. In the absence of such information, dimethylamylamine is subject to the notification requirement in 21 U.S.C. 350b(a)(2) and 21 CFR 190.6. Because the required notification has not been submitted, your products are adulterated under 21 U.S.C. 342(f)(1)(B) and 350b(a).

Even if the required notification had been submitted, we know of no evidence that would establish that your product is not adulterated. In the absence of a history of use or other evidence of safety establishing that dimethylamylamine, when used under the conditions recommended or

suggested in the labeling of your products, will reasonably be expected to be safe, Hemo Rage Black, Lipo-6 Black Ultra Concentrate, Lipo-6 Black, Lipo-6 Black Hers Ultra Concentrate, and Lipo-6 Black Hers are adulterated under 21 U.S.C. 342(f)(1)(B) and 350b(a) because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v). To the best of FDA's knowledge, there is no history of use or other evidence of safety establishing that dimethylamylamine will reasonably be expected to be safe as a dietary ingredient. In fact, dimethylamylamine narrows the blood vessels and arteries, which increases cardiovascular resistance and frequently leads to elevated blood pressure. This rise in blood pressure may increase the work of the heart such that it could precipitate a cardiovascular event, which could range from shortness of breath to tightening of the chest and/or a possible myocardial infarction (heart attack). Therefore, in the absence of a history of use or other evidence of safety establishing that dimethylamylamine is reasonably expected to be safe under the conditions recommended or suggested in the labeling of Hemo Rage Black, Lipo-6 Black Ultra Concentrate, Lipo-6 Black, Lipo-6 Black Hers Ultra Concentrate, and Lipo-6 Black Hers, your products are deemed to be adulterated under 21 U.S.C. 342(f).

It has come to our attention that dimethylamylamine used in products in the dietary supplement marketplace may be produced synthetically. Section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)) defines "dietary ingredient" as a vitamin, mineral, amino acid, herb or other botanical, or dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any dietary ingredient from the preceding categories. Synthetically produced dimethylamylamine is not a vitamin, mineral, amino acid, herb or other botanical. To the best of FDA's knowledge, synthetically produced dimethylamylamine is not commonly used as human food or drink; therefore, it is not a dietary substance for use by man to supplement the diet by increasing the total dietary intake. Further, synthetically produced dimethylamylamine is not a concentrate, metabolite, constituent, extract or combination of a dietary ingredient. Therefore, synthetically produced dimethylamylamine is not a dietary ingredient as defined in section 201(ff)(1) of the Act.

We request that you take prompt action to correct the violations cited above, as well as any other violations associated with your products Hemo Rage Black, Lipo-6 Black Ultra Concentrate, Lipo-6 Black, Lipo-6 Black Hers Ultra Concentrate, and Lipo-6 Black Hers or other products marketed by your firm that contain dimethylamylamine. We also remind you that the new dietary ingredient notification requirement applies to all dietary supplements that contain new dietary ingredients that have not been present in the food supply as articles used for food in a form in which the food has not been chemically altered. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

Failure to immediately cease distribution of your products Hemo Rage Black, Lipo-6 Black Ultra Concentrate, Lipo-6 Black, Lipo-6 Black Hers Ultra Concentrate, and Lipo-6 Black Hers and any other products you market that contain dimethylamylamine could result in enforcement action by FDA without further notice. The Act provides for seizure of violative products and injunction against the manufacturers and distributors of violative products.

We request that you advise us in writing, within 15 days of receipt of this letter, as to the specific steps that have been or will be taken to correct these violations, including any steps taken with respect to product currently in the marketplace. Your response should also include an explanation of each step taken to assure that similar violations do not recur, as well as documentation to support your response. Your written response should be directed to Latasha Robinson, Food and Drug Administration, Center for Food Safety and Applied Nutrition, 5100 Paint Branch Parkway, Office of Compliance (HFS-608), Division of Enforcement, College Park, Maryland 20740-3835. If you have any questions please contact Ms. Robinson at 240-402-1890.

Sincerely,
/S/
Michael W. Roosevelt
Acting Director
Office of Compliance
Center for Food Safety
and Applied Nutrition

Links on this page:

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

JS 44 (Rev. 12/07)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

Pamela Glover and Charles Ellis, individually, and on behalf of all others similarly situated

(b) County of Residence of First Listed Plaintiff Santa Clara, California
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)

Baxter W. Banowsky, Banowsky & Levine, P.C., 12801 N. Cenytral Expressway, Suite 1700, Dallas, TX 75243 (214) 871-1300, (214)

DEFENDANTS

Woodbolt Distribution, Ltd

County of Residence of First Listed Defendant Brazos, Texas
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ❒ 1 U.S. Government Plaintiff
- ❒ 3 Federal Question (U.S. Government Not a Party)
- ❒ 2 U.S. Government Defendant
- ☒ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	☒ 4
Citizen of Another State	☒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury

PERSONAL INJURY
- ❒ 362 Personal Injury - Med. Malpractice
- ☒ 365 Personal Injury - Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 444 Welfare
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 440 Other Civil Rights

PRISONER PETITIONS
- ❒ 510 Motions to Vacate Sentence

Habeas Corpus:
- ❒ 530 General
- ❒ 535 Death Penalty
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition

FORFEITURE/PENALTY
- ❒ 610 Agriculture
- ❒ 620 Other Food & Drug
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 630 Liquor Laws
- ❒ 640 R.R. & Truck
- ❒ 650 Airline Regs.
- ❒ 660 Occupational Safety/Health
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Mgmt. Relations
- ❒ 730 Labor/Mgmt.Reporting & Disclosure Act
- ❒ 740 Railway Labor Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 463 Habeas Corpus - Alien Detainee
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ❒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 810 Selective Service
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 875 Customer Challenge 12 USC 3410
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 892 Economic Stabilization Act
- ❒ 893 Environmental Matters
- ❒ 894 Energy Allocation Act
- ❒ 895 Freedom of Information Act
- ❒ 900Appeal of Fee Determination Under Equal Access to Justice
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from another district (specify) ❒ 6 Multidistrict Litigation ❒ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
28 U.S.C. 1332

Brief description of cause:
Action related to marketing and sale of dangerous drug/dietary supplements

VII. REQUESTED IN COMPLAINT:

☑ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☑ Yes ❒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE 07/20/2012

SIGNATURE OF ATTORNEY OF RECORD /s/ Baxter W. Banowsky

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity**. Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.