Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Rockville, MD 1515 '03 AUG 11 P1:07

In re: Current Good Manufacturing	)	
Practice in Manufacturing,	)	
Packaging, or Holding	)	**Docket No. 96N-0417**
Dietary Ingredients and	)	
Dietary Supplements	)	

COMMENTS OF ESSENTIAL NUTRITION, LTD.; LIFE ENHANCEMENT PRODUCTS, INC.; DURK PEARSON AND SANDY SHAW; JULIAN M. WHITAKER, M.D.; ADVOCARE INTERNATIONAL, L.P.; VITAMIN RESEARCH PRODUCTS; LIVRON VITAMIN CO., INC. AND AMERICAN NUTRITION CORPORATION

Essential Nutrition, Ltd.; Life Enhancement Products, Inc.; Durk Pearson and Sandy Shaw; Julian M. Whitaker, M.D.; Advocare International, L.P.; Vitamin Research Products; Livron Vitamin Co., Inc. and American Nutrition Corporation (hereinafter, collectively, the "Joint Commenters") hereby submit their comments in response to the proposed rule in the above-referenced docket, 68 Fed. Reg. 12158 (March 13, 2003) (hereinafter the "Proposed Rule").

I. BACKGROUND AND INTERESTS OF THE JOINT COMMENTERS

Essential Nutrition, Ltd: Essential Nutrition, Ltd., a company based in East Yorkshire, England, manufactures a wide range of health foods and dietary supplements for numerous companies, including several that sell dietary supplements in the United States. The company is family run and would qualify as a "very small" company under FDA's definition at 68 Fed. Reg. 12,158, 12,153. Essential Nutrition would be directly and adversely affected by the Proposed Rules because of the high costs of compliance and the uncertainty of knowing whether its efforts at compliance would satisfy certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

Life Enhancement Products, Inc.: Life Enhancement Products, Inc. ("Life Enhancement"), a California company, manufactures and sells a wide variety of dietary supplements for human and animal use. Life Enhancement qualifies as a "small" company under the Proposed Rules. The company has a direct interest in the nature and outcome of these proceedings. As a manufacturer of dietary supplements, the company would be subject to high costs of compliance under the Proposed Rule and the uncertainty of knowing whether its efforts at compliance would satisfy certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

Durk Pearson and Sandy Shaw: Pearson and Shaw are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are the authors of four books on aging and age-related diseases, including the number one, million-plus copy best seller ***Life Extensions: A Practical Scientific Approach*** (1982). They have also published three other health books, two of which were best sellers: ***The Life Extension Companion*** (1984); ***The Life Extension Weight Loss Program*** (1986); and ***Freedom of Informed Choice—FDA v. Nutritional Supplements*** (1993). The companies that are licensed to manufacture and sell Pearson and Shaw's formulations fear that the cost of compliance with the Proposed Rule will force them to reduce their product lines or go out of business, thereby causing Pearson and Shaw to experience reduction in, or total loss of, royalty income. They also seek change in certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

Julian M. Whitaker, M.D.: Julian M. Whitaker, M.D. is a physician licensed to practice medicine in the states of California and Washington. He graduated from

Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University of California Medical School. From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: ***Reversing Heart Disease*** (1985), ***Reversing Diabetes*** (1987), ***Reversing Health Risk*** (1989), ***Natural Healing*** (1994), and ***What Your Doctor Won't Tell You About Bypass*** (1995). Since 1991 he has been the editor of ***Health and Healing***, currently the nation's largest single editor health newsletter. In 1998, ***Health and Healing*** had over 500,000 subscribers. He receives royalties from the distribution and sale of a wide variety of dietary supplements based on formulas he develops and licenses. Like Pearson and Shaw, Dr. Whitaker fears that the high cost imposed by the Proposed Rule on his licensee will force either a reduction in products or a closure of the business, thereby reducing or eliminating his royalty income. He also seeks change in certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

Advocare International, L.P.: Advocare is a Texas company engaged in the manufacture and sale of world-class nutritional supplements. Advocare would qualify as a "small" company under the Proposed Rule. Advocare has a direct interest in the outcome of these proceedings because it will be adversely affected by the burdensome costs of the Proposed Rule. Advocare also seeks change in certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

Vitamin Research Products: Vitamin Research Products ("VRP") is a Nevada company that designs, manufactures, and sells a wide variety of high quality dietary

supplements. Under the proposed rules, VRP is a "small" company. VRP has a direct interest in the outcome of these proceedings because it will be adversely affected by the burdensome costs of the Proposed Rule. Advocare also seeks change in certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

Livron Vitamin Company, Inc.: Livron Vitamin Co., Inc. ("Livron") is a New Jersey company engaged in the manufacture and retail sale of dietary supplements. Livron's product line includes a full range of vitamins, minerals, amino acids, and herbal formulations in either tablet or capsule form. Under the Proposed Rule, Livron is a "very small" company. As a manufacturer of dietary supplements, the company would suffer from the high economic costs of compliance. Livron also seeks change in certain provisions of the Proposed Rule, as explained herein, that are undefined and ambiguous.

American Nutrition Corporation: American Nutrition Corporation ("ANC") is incorporated in Las Vegas, Nevada and is engaged in the manufacture and distribution of dietary supplements. ANC is a "small" company under the Proposed Rule. The Proposed Rule will increase ANC's costs of production and recordkeeping, decrease the number of products ANC can offer its customers, and reduce ANC's productivity, because it will have to shift staff from production to regulatory compliance matters.

II. SUMMARY OF COMMENT

The Proposed Rule violates applicable provisions of the Food Drug and Cosmetic Act ("FDCA") because it exceeds the scope of FDA's delegated authority. It also violates the Data Quality Act, the Small Business Regulatory Enforcement Act, and the Administrative Procedure Act because it contains a gross overestimation of the benefits, and a gross underestimation of the costs, of the Proposed Rule. See Exhibit 1. It also

violates the Due Process component of the Fifth Amendment because it is unconstitutionally vague.

Unless revised as proposed herein, the Proposed Rule will impose a costly and extensive prior restraint on all in the dietary supplement industry despite the fact that only a few actors in this market are responsible for harms to consumers. See Exhibit 2 at 439-440. Indeed, while drugs harm 226,855 people[1] and kill 1,418 people annually[2] and foods kill over 5,000 people annually[3], supplements are responsible for as few as 12 deaths (and those are attributed entirely to a few manufacturers and a very few products),[4] making it possible to stem the harms through enforcement of existing laws.

The Proposed Rule aims to "prevent irresponsible firms from making and selling adulterated products" but it, like all prior restraints, will only affect those who are law abiding. Bad actors currently in the market who spike dietary supplements with drugs or who intentionally adulterate or misbrand products in flagrant disregard of the severe civil and criminal penalties for such acts (21 U.S.C. §§ 333, 334, and 335a and 18 U.S.C. § 3571) are unlikely to be deterred by the Proposed Rule and, so, can be expected to continue to commit crimes and civil wrongs after the cGMPs are adopted. The solution to their misdeeds lies in enforcement action under the FDCA's extant adulteration and misbranding provisions, 21 U.S.C. §§ 342 and 343. Thus, the cGMPs will principally, if

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[1] This calculation includes minor, moderate, and major incidents as reported in Litovitz, et.al, 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System, *Am J Emerg Med.* 2002 Sep;20(5):437-443 (Exhibit 2). The drug categories considered were analgesics, anticonvulsants, antidepressants, antihistamines, antimicrobials, asthma therapies, cardiovascular drugs, hormones, muscle relaxants, and sedatives.

[2] As discussed in footnote 1, supra, the drug categories involved in this calculation are analgesics, anticonvulsants, antidepressants, antihistamines, antimicrobials, asthma therapies, cardiovascular drugs, hormones, muscle relaxants, and sedatives. See Exhibit 2.

[3] See, e.g., Centers for Disease Control and Prevention, Food-Related Illness and Death in the United States (1999), www.cdc.gov/ncidod/eid/vol5no5/mead.htm (last visited August 6, 2003)(Exhibit 3).

[4] See, Exhibit 2 at 439-440 (6 of the 12 reported deaths resulted from consumption of ephedra-based products, and 2 deaths were based on an "unknown supplement/homeopathic").

not exclusively, affect the law-abiding. The cGMPs thus hold the greatest promise in having an effect in instances where ignorance and benign negligence result in unintentional safety risks, but that promise is belied by the ambiguities in the Proposed Rule. Those ambiguities prevent manufacturers from comprehending many of the specific measures that FDA may expect for compliance. It would behoove the agency to recognize that point soberly, and make significant revisions to the Proposed Rule to rid it of ambiguous provisions and to reduce its adverse economic effects, as specifically recommended below in these comments.

The Proposed Rule operates on the unrealistic assumption that its adoption will arrest all acts of adulteration and misbranding. See 68 Fed. Reg. 12164 ("The proposed rule governing CGMP requirements for dietary supplements address [sic] manufacturing controls to ensure that dietary ingredients and dietary supplements are produced in a manner that will not adulterate or misbrand such products"). cGMPs afford no such assurance. They do not arrest crime *ex ante*. See www.fda.gov/bbs/topics/NEWS/2002/NEW00809.html; www.fda.gov/foi/warning_letters/g3405d.htm; www.fda.gov/foi/warning_letters/g1400d.pdf. In short, the Proposed Rule can work best to guide the unwary and the negligent toward good behavior.

If the Proposed Rule is not modified in the material respects explained below, it threatens to eliminate a large number of firms that have no prior history of selling dietary supplements or dietary ingredients that have harmed consumers, particularly small firms ($5 million in annual revenues or less, comprising about 88.9% of the market[5])and

[5] Exhibit 4: Nutrition Business Journal Chart "Top 104 U.S. Supplement Manufacturers in 2001." The Commenters created the category of "small firm" based on firm income and it is not directly comparable to the categories (i.e., "very small" or "small") the Proposed Rule creates based on number of employees. 68 Fed. Reg. 12237.

intermediate sized firms ($5 million to $ 99 million in annual revenues, comprising about 9.2% of the market[6]), and to enhance the market position of large firms.[7] The small and intermediate-sized firms lack the financial wherewithal to make all of the changes the Proposed Rule would require, including, *inter alia*, new plant design and construction; the hiring of new personnel and the institution of new personnel training; and extensive new batch testing of materials previously tested by source manufacturers.

The Proposed Rule is peppered with ambiguous aspirational language that affords FDA enforcement officers virtually unbridled discretion in requiring changes to virtually every aspect of production. There is no limit in the Proposed Rule on the exercise of an FDA enforcement officers' discretion. Consequently, the Proposed Rule invites arbitrary and capricious enforcement without regard to the economic consequences of FDA compliance demands on the subjects of cGMP inspection. Interpreting ambiguous provisions differently, an FDA enforcement officer in one part of the country may cause a plant to be subjected to extensive and costly compliance demands that an FDA enforcement officer in another part of the country may elect not to impose (despite substantial similarity in the two plants). The Joint Commenters herein propose specific changes to reign in that discretion by eliminating ambiguities in the Proposed Rule.

Based on the empirical evidence attached and the legal and practical considerations explained below, the Joint Commenters urge the agency to modify the Proposed Rule to eliminate the law violations, to reduce unnecessary economic burdens

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[6] Exhibit 4: Nutrition Business Journal Chart "Top 104 U.S. Supplement Manufacturers in 2001." As with the small firms category described in footnote four, the Commenters created the category "intermediate firm" based on firm income and it is not directly comparable to the categories the Proposed Rule creates based on number of employees. 68 Fed. Reg. 12237.

[7] Indeed, as the attached economic report of Paul Rubin explains, the resulting effects include market consolidation and a likely increase in consumer prices for dietary supplements. See Exhibit 1.

and anticompetitive effects, to eliminate ambiguities that invite the exercise of unbridled discretion by enforcement officers, and to achieve greater assurance of public health protection without culling from the market small and intermediate sized dietary supplement firms.

III. COMMENT

A. SUMMARY OF REQUESTED REVISIONS TO PROPOSED RULE

The Joint Commenters seek reformation of the proposed cGMPs. In particular:

(1) The Joint Commenters request that FDA modify the Proposed Rule to limit the taking of enforcement action against a party for violation of the cGMPs to instances where FDA has proven that the dietary supplement or dietary ingredient in question "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use" in accordance with 21 U.S.C. § 342(f)(1)(A)(i)(ii).

(2) They further request that the agency make the following specific changes (as explained in detail below) to eliminate ambiguities that invite the exercise of unbridled discretion by enforcement officers, resulting in the imposition of unnecessary and potentially overwhelming costs on the subjects of cGMP investigations: (a) include at the end of 111.1 the following: "Violations of the regulations in this part are subject to enforcement action when they cause dietary supplements or dietary ingredients to 'present[] a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary

conditions of use;'" (b) revise 111.12 to eliminate subpart (a) thereof; (c) revise 111.13 to eliminate subpart (a) thereof; (d) revise 111.15(e) to eliminate therefrom the phrase, "of an adequate size and design and be adequately installed and maintained to;" (e) revise 111.15(g) to eliminate therefrom the phrase, "adequate, readily accessible;" (f) revise 111.15(h) to eliminate therefrom the phrase, "that are adequate, convenient, and furnish running water at a suitable temperature. You must do this by;" (g) revise 111.15(h)(1) to eliminate therefrom the phrase, "at each location in your physical plant;" (h) revise 111.20 to eliminate therefrom subpart (a); (i) revise 111.20(d)(6) to eliminate therefrom the phrase, "are adequately unobstructed and of adequate width to;" (j) revise 111.25(a)(1) to eliminate therefrom the phrase, "that are of appropriate design, construction, and workmanship to enable them to be," the word "adequately" before the word "cleaned," and the word "properly" before the word "maintained;" (k) revise 111.25(a)(2) to eliminate therefrom the phrase, "of appropriate design and construction so" and the word "use" before the word "will;" (l) revise 111.65(c) to eliminate the phrase, "but are not limited to;" and (m) revise 111.70(b) to eliminate the phrase, "but are not limited to."

(3) They further request that the Proposed Rule be modified to provide expressly for the protection of trade secrets and confidences. In particular, FDA inspectors made privy to methods of manufacture, formulation, marketing, sales, and distribution should hold that information in strictest confidence as trade secrets and/or confidences, not revealing that information to any third party, so as to encourage full disclosure by companies to FDA but at the same time to ensure that

competitors do not gain an unfair advantage simply by relying on disclosure of trade secrets from FDA cGMP inspections.

(4) They further request that the agency postpone the effective date for the Proposed Rule to 24 months after the rule's adoption to permit the institution of a program of voluntary inspection and compliance and to lessen the economic impact of the rule. Under the proposed program, companies could invite FDA inspection (without risk of penalty for cGMP violations found (unless the violation presented a significant or unreasonable risk of illness or injury)) to determine the extent to which compliance with the cGMPs can be achieved in any particular case. FDA, in turn, would apprise the companies of cGMP noncompliance. The company in question would then have a voluntary option to correct the problems before implementation of the rule (unless the problem presented a significant or unreasonable risk of illness or injury, in which case immediate compliance would be required). FDA would then acknowledge compliance following an investigation to confirm corrective measures. FDA should allow the companies in question to inform the public of that acknowledgment until such future time, if ever, when the agency notifies the company of an act of noncompliance. This approach will create a strong incentive for voluntary compliance in advance of the rule's implementation date and will permit companies to spread out over time the costs of compliance, thereby lessening the economic impact.

(5) They further request that the Proposed Rule be amended to cause FDA, post-final rule implementation, to issue to companies that have been found to comply with the cGMPs certificates to that effect that may be placed on the

companies' dietary supplement or dietary ingredient product labels and in product labeling, thereby creating a free market incentive favoring compliance that would be driven by consumer preference for products so certified.

(6) They further request that in specific instances where there is not a significant or unreasonable risk of illness or injury (and, thus, under the restriction above no basis for taking enforcement action) but in which the agency suspects a violation of the cGMPs that FDA adopt the following approach: (a) that the agency serve written notice to the party in question of the violation and the reasons therefore; (b) that the agency specify precisely what changes are desired to comply with the cGMPs ("Desired Changes") and a reasonable deadline for response to the notice but not for compliance, encouraging a dialogue with the agency on economically feasible means for the company to attain compliance (including extended timetables for achieving compliance and alternative, less costly means for doing so); (c) that the response afford the subject of the notice a reasonable opportunity to explain the economic impact of compliance on the subject and to propose alternative, less costly means to remedy the alleged violation; and (d) that the agency permit the subject a reasonable time to institute the less costly means and verify the utility of the means (including within FDA's timetable for compliance a preference for more time in instances where economic hardship is likely to result from a demand for more rapid compliance).

(7) They further request that FDA state clearly in its final rule that it will not take enforcement action (will not issue an enforcement demand, as hereinafter defined) and will not deem "adulteration," but will rely on a written request for

correction of, any rule violation involving insufficient record-keeping or documentation as required under the Proposed Rule unless it also finds proof of a dietary supplement or dietary ingredient that presents a significant or unreasonable risk of illness or injury.[8]

(8) They further request that the Proposed Rule be modified to limit the requirement for ingredient identity, purity, quality, strength, and composition testing to source manufacturers and to require in lieu of testing of each finished batch of the dietary ingredient or dietary supplement specified in 111.35(g)(1) by finished product manufacturers, packers, and holders, that those "down stream" entities hold certificates of assurance from the source manufacturers confirming compliant testing on the batch of source material and retain documentation of a chain of custody from the source to the market proving processing without exposure to contaminants or other risk of adulteration. Only when the chain of custody has been broken by exposure to contaminants or other risk of adulteration should the dietary ingredients or dietary supplements in question be subject to new confirmatory testing of each finished batch.

B. THE PROPOSED RULE CONFLICTS WITH EXISTING LAWS

As explained below, the Proposed Rule violates the dietary supplement and dietary ingredient safety provisions of the FDCA, 21 U.S.C. § 342(f)(1)(A)(i)(ii), which place the burden of proof on FDA to establish that a dietary supplement or dietary

[8] It is grossly misleading to consumers to call a product "adulterated" if it fails to satisfy the CGMP requirements for documentation or record-keeping. The common understanding of "adulteration" is that the product is contaminated or otherwise defective.

ingredient "presents a significant or unreasonable risk of illness or injury"[9] before the product may be removed from the market on safety grounds. The Proposed Rule effectively reverses that statutory presumption by imposing a broad prior restraint wherein parties are compelled to comply without the agency first establishing a significant or unreasonable risk of illness or injury. That violation can be remedied by modifying the Proposed Rule to require that FDA, before taking any enforcement action against a party for violating the cGMPs, establish that the violation presents a significant or unreasonable risk of illness or injury.

The Proposed Rule violates the Data Quality Act, Pub. L. No. 106-554, 114 Stat. 2763A-153-154 (DQA), the Regulatory Flexibility Act, Pub. L. No. 96-354, 94 Stat. 1164-70 (codified at 5 U.S.C. §§ 601-612) (RFA), the Small Business Regulatory Enforcement Fairness Act, Pub. L. No. 104-121, 110 Stat. 857-74 (SBREFA), and the Administrative Procedure Act, 5 U.S.C. § 706(2)(a) (APA) because it contains a gross underestimation of the economic costs of the Proposed Rule on the regulated class (including, most particularly, the economic impact on small businesses which will bear a disproportionate burden under the Proposed Rule) and a gross overestimation of the economic benefit of the Proposed Rule for the consuming public which will likely see little change in the relative level of safety of products in the market. The attached cGMP Economic Impact Assessment of economist Paul H. Rubin explains in detail that while the Proposed Rule finds annual costs to the regulated class to be no more than $86 million, actual costs are likely to be at least $860 million, and that while the Proposed

[9] Of course a company can not and should not be held responsible for any injuries that may result from use or dosage intake specifically contrary to the specific indications for use displayed on the label or in the labeling of a product.

Rule finds annual benefits to be $218 million, actual benefits are likely no more than $13.9 million. See Exhibit 1.

Violation of the DQA, the RFA, and the SBREFA can be remedied through (1) permitting subject manufacturers, packers, and holders to rely on effective means for eliminating identified cGMP violations that are less costly than those recommended by the agency and (2) permitting a timetable for compliance that minimizes adverse economic impacts.

The Proposed Rule would permit imposition of civil and criminal penalties on noncompliers (See, 68 Fed. Reg. 12,158 at 12,171 ("persons subject to regulation under the act and its implementing regulations may face civil or criminal action if they fail to comply with the act or our regulations")), without defining the criminal offense with sufficient definiteness to permit a reasonable understanding in advance precisely what conduct is prohibited. Moreover, that lack of specificity encourages arbitrary and discriminatory enforcement by agency enforcement officers. The Proposed Rule is thus unconstitutionally vague. See, e.g. Kolender v. Lawson, 461 U.S. 352, 357 (1983) (regulations with criminal sanctions "must define the criminal offense with sufficient definiteness that ordinary people can understand what conduct is prohibited and in a manner that does not encourage arbitrary and discriminatory enforcement"). That violation of the Fifth Amendment can be remedied by adopting the particular changes to the rules specified herein, designed to replace ambiguity with reasonable certainty wherever possible.

1. The Proposed Rule Exceeds FDA's Statutory Authority

Under the FDCA, dietary supplements[10] may not be barred from the market unless the FDA carries its burden of establishing that they "present[] a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use." 21 U.S.C. § 342(f)(a)(i)(ii)[11]. Moreover, 21 U.S.C. § 342(f), provides that "in any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated." The agency "must give effect to the unambiguously expressed intent of Congress." Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 843 (1984). The language of the FDCA is plain. The burden of proof lies with the agency to prove a significant or unreasonable risk of illness or injury before it may deny a dietary supplement market access. FDA's regulation of dietary supplements through cGMPs cannot exceed that authority. FDA cannot bar products from the market unless it has met its burden of proof under 21 U.S.C. § 342(f).

Moreover, the FDCA states that should the agency adopt cGMPs for dietary supplements they should be modeled after the food cGMPs. 21 U.S.C. § 342(g)(2);[12] see

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[10] Dietary supplements differ from drugs by definition in that, among other things, they must be "intended to supplement the diet." 21 U.S.C. § 321(ff)(1).

[11] FDA indicates in the Proposed Rule that it has authority to prevent the spread of communicable disease from dietary supplements or dietary ingredients in intrastate and interstate commerce. See Proposed Rule at 12,167. The agency must be mindful of the limits imposed by the Supreme Court in United States v. Lopez, 514 U.S. 549, 557 (1995) (FDA may only regulate intrastate activity that has a "substantial effect" on interstate commerce and activity that "exerts a substantial economic effect on interstate commerce").

[12] That section states:

> The Secretary may be regulation prescribe good manufacturing practices for dietary supplements. Such regulations shall be modeled after current good manufacturing practice regulations for food any may not impose standards for which there is no current and generally available analytical methodology. No standards of current good manufacturing practice may be imposed unless such standard is included in a regulation promulgated after notice and opportunity for comment in accordance with chapter 5 of title 5, United States Code. 21 U.S.C. § 342(g)(2).

also 68 Fed Reg. at12159. In point of fact the Proposed Rule for cGMPS for dietary supplements is modeled after the drug cGMPs not those for food. For example, the food cGMPs, 21 C.F.R. § Part 110, do not require the extensive batch testing required by the Proposed Rule (proposed sections 111.35 through 111.65). By contrast, the drug cGMPs, 21 C.F.R. Part 210, have extensive batch testing requirements (in subpart E) akin to those in the Proposed Rule. Thus the Proposed Rule conflicts with Congress' delegation of authority to the agency to promulgate cGMPs for dietary supplements in accordance with food cGMPs. The scope of the Proposed Rule's requirements exceed the authority Congress granted to FDA to promulgate cGMPs for dietary supplements.

Drugs, not dietary substances, are often synthetic substances foreign to the body commonly with adverse effects and may not enter the market until FDA has received substantial evidence of their efficacy (21 U.S.C. § 355 (d)(7)) and safety. 21 U.S.C. § 355(d)(1). Unlike in the dietary supplement context, in the drug context the proponent of the drug, not the government, bears the burden of proof to establish efficacy and to show the drug safe via adequate tests by all methods reasonably applicable. 21 U.S.C. § 355(d). FDA may not lawfully take enforcement action against a dietary supplement manufacturer, distributor, or seller unless it finds the violation in question causes a dietary supplement or dietary ingredient to "present a significant or unreasonable risk of illness or injury," 21 U.S.C. § 342(f)(1)(A). Thus, it may neither declare a supplement adulterated nor interfere with its marketability solely on the basis of a cGMP violation, such as inadequate recordkeeping, unless it also proves a significant or unreasonable risk of illness or injury.

For example, if an FDA inspector, under sections 111.15 and 111.45 of the Proposed Rule, informed a small manufacturer of a dietary supplement that the manufacturer failed to maintain required records[13] or needed to have its plant reconstructed to include new plumbing for additional hand-washing stations located in closer proximity to human contact points in the production line, or needed to have more space between fixed equipment and walls or better lighting or better plumbing, that request would not rise to the level of a legally enforceable demand unless the agency also had evidence that a dietary supplement or dietary ingredient manufactured by the company presented a significant or unreasonable risk of illness or injury as a direct result of those cGMP violations. Without that additional evidence, FDA has no lawful power under the FDCA either to compel the manufacturer to comply or to hinder or prevent the manufacturer from selling dietary supplements. **FDA should therefore not equate a cGMP rule violation *per se* with adulteration and misbranding.**

Nevertheless, every request from FDA following a cGMP inspection will likely be taken by the subject of it as a legally enforceable one unless notified to the contrary by FDA. Consequently, the FDA needs to distinguish clearly between those, what we might call, "demands" that are enforceable and those, what we might call, "requests" that are not and to compel compliance only for the former and to recommend, but not compel, compliance for the latter (much as FDA now does when it issues so-called "warning"

[13] If FDA equates failure to meet record-keeping requirements with adulteration there is a great risk that the public will misapprehend the charge, thinking the products at issue are unsafe. FDA should not state an adulteration charge unless a product meets the statutory definition of adulteration. Moreover, the U.S. Court of Appeals for the District of Columbia in Pearson v. Shalala 164 F.3d 650, 658 (D.C.Cir. 1998) did not follow the Ninth Circuit decision, Ass'n of Nat'l Advertisers v. Lungren, 44 F.3d 726, 736 (9th Cir. 1994), wherein the Ninth Circuit allowed the government to prescribe meaning to a common term that differed from the term's common meaning. This agency is under an executive order to adopt regulations using terms that do not deviate from their plain meaning. Regulatory Planning and Review, Exec. Order No. 12,866, 58 Fed. Reg. 51,735 (September 30, 1993).

letters (where compliance is on pain of enforcement) and "courtesy" letters (where enforcement is not presently planned by the agency). The FDA should make the distinction transparent such that the subject of a cGMP investigation is aware of the presence or absence of a legally enforceable demand. This change will also enable those who receive "requests" from FDA to budget for revisions over time, cognizant that they are not facing a "demand" where compliance must be achieved immediately on pain of enforcement action. The Proposed Rule needs to be modified to incorporate the foregoing distinction and to ensure that it is made known routinely to every subject of a cGMP investigation that receives a post-investigation demand or request from the agency.

2. The Proposed Rule Violates the Data Quality Act, the Regulatory Flexibility Act, the Small Business Regulatory Enforcement Fairness Act, and the Administrative Procedure Act because It Underestimates Costs and Overestimates Benefits

As explained below (and in the economic report attached as Exhibit 1), the regulatory flexibility analysis in the Proposed Rule is fundamentally flawed because it greatly underestimates costs, overestimates benefits, and fails to evaluate the extent to which, and compensate for the fact that, the Proposed Rule imposes a disparate economic burden upon small and intermediate sized firms in the dietary supplement industry. The Proposed Rule thus fails to fulfill the requirements of the DQA, the RFA, the SBREFA, and the APA.

The Data Quality Act. As required by the Data Quality Act, Pub. L. No. 106-554, 114 Stat. 2763A-153-54, (DQA) the Department of Health and Human Services (DHHS) has promulgated guidelines for ensuring the quality, objectivity, utility, and integrity of information disseminated by the FDA. www.hhs.gov/infoquality; see also 67

Fed. Reg. 61343-44. DHHS recognizes that rulemaking documents and explanatory material published in the Federal Register are subject to the requirements of the DQA. It confirms that FDA must rely on objective data, i.e., data which is "accurate, clear, complete, and unbiased." www.hhs.gov/infoquality/fda.html. It must also ensure "transparency" of "influential scientific, financial, and statistical information." Id. "Influential" information of this kind is that which is "expected to have an annual effect on the economy of $100 million or more or will adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities." Id.

The Proposed Rule violates the Data Quality Act because it does not rely on objective data. Throughout its cost and benefit analyses the agency relies upon inaccurate assumptions and false conclusions. See, e.g., Exhibit 1 at 5, 7, 9. The agency makes the assumption that only one in 100 events is reported but that multiplier is unacceptable and based on a false premise. Id. at 7-8. The agency creates upward bias by assuming that if the Proposed Rule were in place there would be no recalls. Id. at 10. Clearly that assumption is an impossibility in light of the frequent recalls in the drug industry where GMPs have been in place for years. Id. at 10. The Proposed Rule lacks transparency in that it invents a variable to calculate reduced costs as a benefit but the variable created is not real. Id. at 11. It ignores set-up and start-up costs without explanation, resulting in a gross underestimate of the Propose Rule's costs to the industry. Id. at 12. Finally, and perhaps most egregiously, the Proposed Rule engages in clear double counting of the one event that drives the entire analysis of the cost of recalls and the calculation of reduced chance for catastrophic events. Id. at 2 and 7. Thus,

"there is no plausible evidence that a rule would provide any significant benefits." Exhibit 1 at 16. The costs of the Proposed Rule are vastly greater than its benefits. Id. The cost-benefit analysis provided in the Proposed Rule is so seriously flawed as to be "virtually worthless." Id. at 16.

The Regulatory Flexibility Act. Congress enacted the Regulatory Flexibility Act (RFA) because "uniform Federal regulatory and reporting requirements have in numerous instances imposed unnecessary and disproportionately burdensome demands . . . upon small businesses, small organizations, and small governmental jurisdictions with limited resources" and because "the failure to recognize differences in the scale and resources of regulated entities has in numerous instances adversely affected competition in the marketplace, discouraged innovation, and restricted improvements in productivity." Regulatory Flexibility Act of 1980, Pub. L. No. 96-354, 94 Stat. 1164 (codified at 5 U.S.C. §§ 601-612). The RFA requires, *inter alia,* "a description of any significant alternatives to the proposed rule which accomplish the stated objectives of applicable statutes and which minimize any significant economic impact of the proposed rule on small entities." 5 U.S.C. 603(c).

The Proposed Rule violates the RFA because, as Professor Rubin concludes in his economic report (attached as Exhibit 1), the adverse economic effects of the rule will fall hardest on small firms because of the fixed nature of regulatory costs making them independent of the size of the firm. Exhibit 1 at 18. Professor Rubin states that the Proposed Rule will reduce demand and sales of supplements greatly. The costs of the proposed rule, significantly outweighing its benefits, will cause increased prices which will cause a reduced demand. Id. The impact of the reduced demand is exacerbated in

small firms having per unit basis costs that are far more affected by increased fixed regulatory costs. Id. at 18-19. The Proposed Rule fails to "recognize differences in the scale and resources of regulated entities." The Proposed Rule has a disproportionate effect upon small firms, thus violating the RFA.

The Small Business Regulatory Enforcement Fairness Act. The Small Business Regulatory Enforcement Fairness Act (SBREFA) amended the RFA to permit judicial review of every final agency regulatory flexibility analysis. 5 U.S.C. § 611. The SBREFA requires the agency's final regulatory flexibility analysis to include, *inter alia*, (1) a summary of the significant issues raised by the public comments in response to the initial regulatory flexibility analysis, a summary of the assessment of the agency of such issues, and a statement of any changes made in the proposed rule as a result of such comments and (2) a description of the steps the agency has taken to minimize the significant economic impact on small entities, including a statement of the factual, policy, and legal reasons for selecting the alternative adopted in the final rule and why each of the other significant alternatives to the rule was rejected. 5 U.S.C. §§ 604(a)(1-5). Thus, the Proposed Rule's violation of the RFA described in the preceding section is reviewable by the courts in a private right of action.

The Administrative Procedure Act. The U.S. Court of Appeals for the D.C. Circuit has held that a party's comment on the regulatory flexibility analysis of an agency is independently reviewable as part of the assessment of the overall reasonableness of the rule that begot that analysis. Small Refiner Lead Phase-Down Task Force v. EPA, 705 F.2d 506, 537 (D.C. Cir. 1983). Indeed, our Court of Appeals has held that "a reviewing court should consider the regulatory flexibility analysis as part of its overall judgment

whether a rule is reasonable and may, in an appropriate case, strike down a rule because of a defect in the flexibility analysis." Id. at 539; See also Mid-Tex Electric Cooperative, Inc. v. Federal Energy Regulatory Commission, 773 F.2d 327, 341 (D.C. Cir. 1985). Thus, the APA creates a private right of action when an agency has a defect in its regulatory flexability analysis. Agency action without reasoned explanation or based on insufficient evidence is arbitrary and capricious under the APA. 5 U.S.C. § 706(2)(A); e.g., North Germany Area Council v. FLRA, 805 F.2d 1044 (D.C.Cir. 1986)(agency lacked reasoned explanation for its action); Almay Inc. v. Califano, 569 F.2d 674 (D.C.Cir. 1977)(agency action was based on insufficient evidence). As discussed above in this subsection, the regulatory flexability analysis of the Proposed Rule is seriously flawed and thus violates the APA. The Proposed Rule is based on insufficient evidence and its reasoning, albeit lengthy, is defective, based on repeated erroneous cost/benefit calculations, assumptions and conclusions as discussed in Exhibit 1. Thus, the Proposed Rule violates the APA because it is arbitrary and capricious agency action not otherwise in accordance with the law. 5 U.S.C. 706(2)(A).

3. The Proposed Rule Violates the Fifth Amendment Void for Vagueness Doctrine and the APA Prohibition on Unconstitutional Agency Action because It Fails to Define How to Achieve Compliance with Requisite Specificity

The Proposed Rule states that "persons subject to regulation under the act and its implementing regulations may face civil or criminal action if they fail to comply with the act or our regulations." 68 Fed. Reg. 12,158, 12171 (March 13, 2003). Because the Proposed Rule carries such sanctions (and particularly because it holds out the possibility of criminal penalties for rule violation), it must "clearly define" all prohibited acts such that the regulated class is given "fair notice that [its] contemplated conduct is forbidden."

Grayned v. City of Rockford, 408 U.S. 104, 108 (1972); Papachristou et al. v. City of Jacksonville, 405 U.S. 156, 162 (1972). The law must provide "explicit standards for those who apply them" so that it avoids "arbitrary and discriminatory enforcement." Grayned, 408 U.S. at 108. If "'men of common intelligence'" are left to guess at [the law's] meaning," then the law is unconstitutionally vague under the Fifth Amendment. See Connally v. General Construction Co., 269 U.S. 385, 391 (1926). The regulated must know when they are "in danger of triggering an adverse reaction" or else the law is unconstitutionally vague. Timpinaro v. SEC, 2 F.3d 453, 460 (D.C. Cir. 1993). Moreover, agency actions that are "contrary to constitutional right, power, privilege, or immunity" violate the APA. 5 U.S.C. 706(2)(B); e.g., Porter v. Califano, 592 F.2d 770 (5th Cir. 1979)(reviewing action suspending agency employee in violation of due process rights). Thus agency regulation that is void for vagueness also violates the APA. Such is the case with the Proposed Rule.

Despite the very limited nature of proven harm in the dietary supplement market, the Proposed Rule imposes a broad and extensive regulatory regime on all dietary supplement manufacturers, packers, and holders, affecting (1) personnel; (2) physical plants; (3) equipment and utensils; (4) production and process controls; (5) holding and distributing; (6) consumer complaints related to good manufacturing practices; and (7) records and record-keeping. The cGMPs impose many largely aspirational and undefined and, therefore, ambiguous requirements. For example, proposed rule 111.12(a)(1) would require "*qualified* employees" (but qualifications are undefined); proposed rule 111.13(a) would require "an *adequate* number of *qualified* personnel to supervise . . . manufacturing, packaging, or holding" (but what constitutes "adequate" and what

constitutes "qualified" are undefined); proposed rule 111.15(e) would require physical plant plumbing to "be of an *adequate* size and design" and to "*adequately* installed and maintained" (but what constitutes "adequate" in those contexts is left undefined); proposed rule 111.15(g) would require that physical plants have "*adequate, readily accessible* bathrooms" (but what constitutes "adequate" and "readily accessible" is left undefined); proposed rule 111.15(h) would require "hand-washing facilities that are *adequate, convenient,* and furnish running water at a *suitable* temperature" (but what constitutes an "adequate, convenient" hand washing facility and what constitutes a "suitable" temperature is left undefined); proposed rule 111.15 (h)(1) would require "hand-washing and, where appropriate, hand-sanitizing facilities at each location in your plant where good hygienic practices required employees to wash or to sanitize or both wash and sanitize their hands" (but in light of the fact that one can never be "too hygienic" we are left to guess how many such locations would an FDA investigator insist exist in any plant); proposed rule 111.20(a) requires that the physical plant "be *suitable* in size, construction, and design" (but what constitutes "suitable" is left undefined); proposed rule 111.20(b) requires that the physical plant have "*adequate* space for orderly placement of equipment and holding materials as is *necessary* for maintenance, cleaning, and sanitizing operations" (but what constitutes "adequate" and what is "necessary" is left undefined); proposed rule 111.20(d)(6) requires "aisles or working spaces between equipment and walls that are *adequately unobstructed* and of *adequate width*" (but what constitutes "adequate" in those circumstances is left undefined); proposed rule 111.20(e) requires "*adequate* light" in various parts of the plant (but what constitutes "adequate" is left undefined); and proposed rule 111.25(a)(1) requires use of "equipment and utensils

that are of *appropriate design, construction, and workmanship* to enable them to be *suitable* for their intended use and to be *adequately cleaned* and *properly maintained*" (but what is "appropriate," "suitable," and "adequate" is not defined). See Proposed Rule (emphasis added throughout).

In the Proposed Rule section 111.12(a) requires "qualified employees" but does not define the term; subpart (b) demands that employees have "the training and experience to perform the person's duties." Presumably subpart (a) is not a redundancy of subpart (b). If that is indeed the case, then subpart (a) is unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA because it is impossible for the subject of the regulation to discern who will be deemed by the FDA a qualified employee absent a clear definition of that term. It likewise provides enforcement officers no limitations on the exercise of their discretion as to what qualifications are sufficient; accordingly, it invites exercise of unbridled discretion and disparate decision-making. For all practical purposes, subpart (b) would seem to suffice without the ambiguous (a) and, so, the Joint Commenters urge FDA to delete subpart (a). Likewise section 111.12(a) requires "qualified personnel to supervise" but does not define the term "qualified personnel;" subpart (b) demands that supervisors be "qualified by training and experience to supervise." Presumably subpart (a) is not a redundancy of subpart (b). If that is indeed the case, then subpart (a) is unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA because it is impossible for the subject of the regulation to discern who will be deemed by the FDA a qualified supervisor absent a clear definition of that term. It likewise provides enforcement officers no limitations on the exercise of their discretion as to what

qualifications are sufficient; accordingly, it invites exercise of unbridled discretion and disparate decision-making. For all practical purposes, subpart (b) would seem to suffice without the ambiguous (a) and, so, the Joint Commenters urge FDA to delete subpart (a).

Section 111.15(e) requires physical plant plumbing to be "of an adequate size and design and be adequately installed and maintained" but does not define the term adequate such that the regulated class can discern its meaning. It is therefore unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA. It also provides enforcement officers no limitations on the exercise of their discretion as to what plumbing will be considered adequate in its size, design, installation, and maintenance; accordingly, it invites exercise of unbridled discretion and disparate decisionmaking. The Joint Commenters therefore urge FDA to delete the phrase, "be of an adequate size and design and be adequately installed and maintained to" from Section 111.15(e). Section 111.15(g) requires bathrooms to be "adequate" and "readily accessible" but defines neither term such that the regulated class can discern its meaning. It is therefore unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA. It also provides enforcement officers no limitations on the exercise of their discretion as to what bathrooms are adequate and readily accessible; accordingly, it invites exercise of unbridled discretion and disparate decisionmaking. The Joint Commenters therefore urge FDA to delete the phrase, "adequate, readily accessible" from Section 111.15(g).

Section 111.15(h) requires hand-washing facilities "that are adequate, convenient, and furnish running water at a suitable temperature" but does not define the terms "adequate," "convenient" and "suitable" such that the regulated class can discern their

meaning. It is therefore unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA. It also provides enforcement officers no limitations on the exercise of their discretion as to what hand-washing facilities are adequate and convenient and what water temperature is suitable; accordingly, it invites exercise of unbridled discretion and disparate decisionmaking. The Joint Commenters urge FDA to delete the phrase, "that are adequate, convenient, and furnish running water at a suitable temperature. You must do this by," from Section 111.15(h). Section 111.15(h)(1) requires hand-washing and, where appropriate, hand-sanitizing facilities "at each location in your physical plant" where good hygienic practices require employees to wash or sanitize their hands. The rule gives the regulated class and enforcement officers no clear understanding as to where such facilities would have to be located in physical plants and thus denies the regulated class sufficient guidance to discern the rule's meaning. It is therefore unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA. It also provides enforcement officers no limitations on the exercise of their discretion as to what locations in a plant must be equipped with hand-washing and hand-sanitizing facilities; accordingly, it invites exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to delete the phrase, "at each location in your physical plant," from Section 111.15(h)(1).

Section 111.20(a) requires every physical plant to "be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations" yet does not define what constitutes "suitable." The rule gives the regulated class and enforcement officers no clear understanding as to what constitutes suitable physical plant

size, construction and design. It is therefore unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA. It also provides enforcement officers no limitations on the exercise of their discretion as to what constitutes suitable physical plant size, construction and design; accordingly, it invites exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to delete subpart (a) of Section 111.20.

Section 111.20(d)(6) requires aisles or working spaces between equipment and walls to be "adequately unobstructed and of adequate width" to permit all persons to perform their duties and to protect against contamination. The rule gives the regulated class and enforcement officers no clear understanding as to what constitutes "adequately unobstructed" and "adequate width." It is therefore unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA. It also provides enforcement officers no limitations on the exercise of their discretion as to what constitutes an adequately unobstructed aisle or working space and as to what constitutes adequate width between an aisle or working space and the wall; accordingly, it invites exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to delete the phrase, "are adequately unobstructed and of adequate width to," in Section 111.20(d)(6).

Section 111.25(a)(1) requires equipment and utensils to be "of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained." The rule gives the regulated class and enforcement officers no clear understanding as to what constitutes "appropriate design, construction, and workmanship," what constitutes "suitable for their intended

use" and what constitutes "adequately cleaned and properly maintained." It also provides enforcement officers no limitations on the exercise of their discretion as to what constitutes appropriate design, construction, and workmanship, what constitutes equipment and utensils suitable for their intended use, and what constitutes adequate cleaning and proper maintenance of equipment and utensils; accordingly, it invites exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to eliminate the phrase, "that are of appropriate design, construction, and workmanship to enable them to be," the word "adequately" before the word "cleaned," and the word "properly" before the word "maintained" in Section 111.25(a)(1).

Section 111.25(a)(2) requires use of equipment and utensils that are of "appropriate design and construction" but does not define those terms. The rule gives the regulated class and enforcement officers no clear understanding as to what constitutes "appropriate design and construction." It also provides enforcement officers no limitations on the exercise of discretion as to what constitutes appropriate design and construction; accordingly, it invites exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to eliminate the phrase, "of appropriate design and construction so" and the word "use" before the word "will" in Section 111.25(a)(2).

Section 111.65(c) requires the taking of necessary precautions to avoid contamination and specifies a listing but precedes that listing with the phrase, "these precautions include, but are not limited to." The phrase "but are not limited to" denies the regulated class and enforcement officers a clear understanding of all precautions that need to be taken. It also provides enforcement officers no limitation on the exercise of

discretion as to what precautions ought be taken; accordingly, it invites the exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to eliminate the phrase, "but are not limited to;" from Section 111.65(c).

Section 111.70(b) requires use of effective means to fill, assemble, package and perform related operations and specifies a listing but precedes that listing with the phrase, "but are not limited to." The phrase "but are not limited to" denies the regulated class and enforcement officers a clear understanding of all effective means that need to be taken. It also provides enforcement officers no limitation on the exercise of discretion as to what effective means ought be taken; accordingly, it invites the exercise of unbridled discretion and disparate decision-making. The Joint Commenters urge FDA to eliminate the phrase, "but not limited to," from Section 111.70(b).

In summary, the Proposed Rule violates the void for vagueness doctrine of the Fifth Amendment and the APA's prohibition against arbitrary and capricious, and unconstitutional, agency action. The Commenters urge the specific changes to the above sections to clarify the rules requirements with adequate specificity.

4. FDA Should Modify the Proposed Rule to Protect Trade Secrets and Confidences

The Proposed Rule necessarily involves FDA for the first time in extensive review of every dietary supplement firm's confidential and trade secret information pertaining to sources, personnel and personnel qualifications, product formulae and manufacturing methods, suppliers, product prices, retailers, business plans, balance sheets, customer lists, complaint files, and other such strategic information useful to competitors.

Disclosure of confidential information by an officer or employee of the federal government when received in an official capacity is a criminal act under the Federal Trade Secrets Act. 18 U.S.C. § 1905.[14] Violation of the Federal Trade Secrets Act creates a private right of action under the APA as agency action not in accordance with law. 5 U.S.C. § 706(2)(A); Serono Labs, Inc. v. Shalala, 35 F.Supp. 2d 1,3 (D.D.C. 1999). Disclosure of such information violates the FDCA's prohibition against any person using to his own advantage or revealing any information concerning any method or process which is a trade secret entitled to protection and acquired under FDCA authority, including in conducting factory inspections pursuant to 21 U.S.C. § 373. 21 U.S.C. § 331(j). Moreover, disclosure of trade secrets and confidences may be a tortious act, depending upon the state in which the tort is committed by the federal defendant, for which sovereign immunity is waived by the Federal Tort Claims Act. 28 U.S.C. § 2672. Finally, all trade secrets and confidences gained by the agency are protected from public disclosure under the Freedom of Information Act. 5 U.S.C. 552(b)(4).

To ensure that dietary supplement manufacturers are informed of their rights and to facilitate their comfort with providing access to such information without reservation or legal encumbrance, FDA should provide the regulated class assurance that all trade

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[14] The Trade Secrets Act states:

> Whoever, being an officer or employee of the United States or of any department or agency thereof, ... publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association; or permits any income return or copy thereof or any book containing any abstract or particulars thereof to be seen or examined by any person except as provided by law; shall be fined not more than $ 1,000, or imprisoned not more than one year, or both; and shall be removed from office or employment.

18 U.S.C. § 1905.

secrets and confidences will be kept from public disclosure during and after the investigation; indeed, indefinitely into the future.[15] Otherwise, the rules will facilitate an invasion of that protected intellectual property and may cause it to enter the public domain to the severe economic detriment and competitive disadvantage of the regulated firms. The Proposed Rule should list the above legal protections and affirm that the agency shall hold all trade secrets and confidences gained from investigations confidential and shall not reveal them to any third party.

B. THE PROPOSED RULE HAS MATERIAL ECONOMIC FLAWS

1. The Proposed Rule's Estimate of Costs and Benefits Is Inaccurate

The regulatory flexibility analysis of benefits stemming from the Proposed Rule lacks an adequate basis to justify the $218 million estimate in that category. In his detailed assessment attached as Exhibit 1, economist Paul Rubin explains that FDA lacks sound empirical evidence upon which to base its estimate of reduced health care costs from elimination of the occurrence of "rare catastrophic events" and from elimination of recalls. See Exhibit 1 at 4, 5-7. Rubin finds that "there is no evidence" to support the reduced health care cost figure, that both the reduced health care cost and recall benefit cost savings estimates depend heavily on an isolated event (the harms accrued from domestic sale of an imported and contaminated batch of L-tryptophan) not shown to recur or to be characteristic of any other dietary supplement, that FDA presumes adulteration requiring recalls will not occur after the cGMPs are in place when no GMPs have arrested instances of adulteration in the drug market where recalls continue to this day, even after decades of drug GMPs, and that FDA's health care cost estimate is "too

[15] Indeed, under the drug application regulations the FDA has affirmed those protections. 21 U.S.C. § 314.430.

speculative to be the basis for sound policy." See Exhibit 1 at 4, 5-7. Economist Rubin also finds evidence of erroneous double counting of figures to achieve the $218 million benefit. See Exhibit 1 at 7. In addition, he finds a "quite strange" calculus dependent entirely on a fiction, the agency's "reduced hypothetical costs" category in its RFA. Rubin concludes that this fictive estimate "is inappropriate to include . . . as part of the benefit of the rule." See Exhibit 1 at 11. Recalculating the benefits based on valid empirical data, Rubin finds the actual benefits "are in the range of $14 million, rather than the $218 million in the Proposed Rule." See Exhibit 1 at 12.

The regulatory flexibility analysis of costs stemming from the Proposed Rule lacks an adequate basis to justify the $86 million estimate in that category. Based on empirical data, including actual cost estimates from three dietary supplement companies, Rubin conservatively estimates the actual costs of the Proposed Rule to be $860 million. See Exhibit 1 at 16.

To ensure compliance with the DQA, the RFA, the SBREFA, and the APA, the final regulatory flexibility analysis must take into account each of the points raised in the Rubin economic impact assessment (attached) and must provide for alternative measures to reduce the adverse economic impacts and anti-competitive effects. The actual costs of $860 million far outweigh the actual benefits of $14 million.

2. The Proposed Rule Is an Excessive Financial Burden on Small and Intermediate Sized Firms and Has Significant Anti-Competitive Effects

The Proposed Rule has a disparate impact on small, and intermediate sized, firms. The dietary supplement marketplace is comprised largely of small and intermediate sized entities. Only 1.9% of the companies in the market have annual incomes in excess of $100 million, i.e., are large firms. See Exhibit 4. Fully 9.2% have annual incomes of

between $5 million and $99 million, i.e., intermediate sized firms. See Exhibit 4. The largest segment, 88.9% of the market, have annual incomes of under $5 million, i.e., are small firms. See Exhibit 4. Thus, when one considers the costs of the Proposed Rule such as hiring new, qualified people; training existing personnel; hiring consultants to help guide companies with the new record-keeping requirements; reconstructing physical plants; and testing every batch of finished dietary ingredient and dietary supplements, there can be no doubt that costs of that kind in the range of $400,000 to $1.75 million pose a threat to the survival of 88.9% of the dietary supplement market having annual incomes of less than $5 million. See Exhibit 4. As Rubin explains in his economic report, only a few large firms can be expected to have the financial wherewithal to meet those costly requirements. Exhibit 1 at 18-19. Indeed, large firms have an incentive to do so, aware that the requirements will eliminate or substantially hinder the market presence of competitors.[16] One of the companies interviewed by Dr. Rubin informed the Joint Commenter's counsel that it had already discontinued its sale of dietary supplement products in anticipation of not being able to afford the costs of the Proposed Rule and is instead focusing on food products because food GMPs are far less onerous than those proposed for dietary supplements.

[16] If competition is reduced through the enforcement of the Proposed Rule, thereby culling small and intermediate sized firms, a secondary effect will be to eliminate speech concerning dietary supplement products' innovative uses. Market entrants have a greater economic incentive for dissemination of new information concerning the effects of foods and supplements than market leaders. To the extent the government gains more direct control over processes used to make dietary supplements and exercises unbridled discretion, regulating what may be sold, it has a strong intimidating effect on a party's exercise of its sales and on the information communicated to facilitate sales. See, e.g., Writers Guild of America, West Inc. v. American Broadcasting Inc., 609 F.2d 355,365 (9th Cir. 1979)("Regulation through 'raised eyebrow' techniques...is commonplace in the administrative context, and in some instances may fairly be characterized...as official action by the agency")(footnotes omitted), cert. denied, 449 U.S. 824 (1980); see also, Writers Guild of America v. FCC, 609 F.2d 355, 365-66 (9th Cir. 1979)("the line between permissible regulatory activity and impermissible raised eyebrow harassment of vulnerable licensees is...exceedingly vague").

Finally, because innovation in product design, safety, and ingredient composition are often the result of small and intermediate sized market entrants attempting to cleave consumers from market leaders, the Proposed Rule will stifle innovation in the market. That will tend to retard, rather than promote, safety. In addition, if enforcement of the Proposed Rule is expensive, large, surviving companies can be expected to expend only so much as FDA requires on product safety and no more. For surviving intermediate-sized firms, the tendency will be to draw from discretionary funds, such as those for research and development, thereby retarding innovation and, consequently, understanding of both ingredient effects and new ways to ensure safety. Thus, the Proposed Rule imposes a significant economic burden and creates anticompetitive effects that will have a substantially negative impact on small and intermediate sized firms.

C. EXPLANATION OF REQUESTED REVISIONS TO PROPOSED RULE TECHNICAL REQUIREMENTS

1. The Proposed Rule's Testing Requirements Exceed Those Reasonably Necessary to Establish Ingredient Identity, Purity, Quality, Strength, and Composition

In Section 111.35(g)(1), the Proposed Rule requires the testing of "each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to determine whether specifications for identity, purity, quality, strength, and composition are met, provided that there are scientifically valid analytical methods available to conduct such testing." The rule operates on the unarticulated assumption that dietary supplements are more like drugs than foods. That is most certainly not the case. By definition, dietary supplements must be ingestible daily and are derived from sources that are consumed as foods or constituents of foods. 21 U.S.C. § 321(ff). Like foods, supplements derived from natural sources will necessarily vary in their strength. An

herbal supplement, for example, may be comprised of crushed leaves that will include various chemical constituents responsible for health enhancing physiological effects. Those constituents will necessarily vary from leaf to leaf because plants in nature do not include identical levels of the various constituents. Consequently, demanding proof of strength, as one would in a standardized drug, makes little sense in the context of dietary supplements derived from plant sources. Moreover, because each dietary ingredient is itself a constituent of a food daily consumed, so long as the source is free of contaminants (has its proper identity, purity, quality, and composition), it may be combined with other such dietary ingredients in a pill and consumed without need for independent testing of the combination. That is because the constituents, as food ingredients, would be capable of being consumed in the daily diet and mixed in the gut cavity without adverse effect. Thus, unlike the mixing of drug substances with other drugs, other foods, or other supplements, the mixing of foods and food ingredients is common in the daily diet and poses no serious threat to public health.

Therefore, FDA may reasonably demand that source ingredients be tested for identity, purity, quality, and composition by source manufacturers—but not strength which may depend on several, sometimes unidentified, compounds. Source manufacturers should be required to certify based on such testing that the ingredients in each finished batch have satisfied the appropriate analytical testing methodology. Those who purchase ingredients from the source manufacturer, however, should not be required to do batch testing thereafter unless there has been a breach in quality control during distribution and subsequent manufacture. If there has been no such breach, and the "down stream" parties have documentation to prove chain of custody and consistent

controls to avoid a change in the status of the source materials from the time of manufacture, then that should suffice without the need for expensive, redundant testing thereafter. That should hold true even if source materials are mixed in a subsequent manufacturing stage. For foods and dietary supplements, this approach is all that is required to ensure safety. The FDA should not demand more; indeed, doing so, creates unnecessary and burdensome costs on the regulated class, falling hardest on small to intermediate-sized firms.

D. ENFORCEMENT OF THE PROPOSED RULE

The dietary supplement market is marked by an extraordinary safety record. See Exhibit 2. The existing statutory enforcement provisions, 21 U.S.C. §§ 333, 334, 335a and 18 U.S.C. § 3571, give FDA all the authority it needs to arrest the harms in the dietary supplement market caused by adulterated products. Unlike drugs that result in 1,418 deaths and harm to 226,855 consumers annually (Exhibit 2, note 1 supra) and foods, which take over 5,000 lives annually (Exhibit 3, note 2 supra), dietary supplements rarely cost the lives of anyone, Exhibit 2 (note 3 supra), and when they do the suspects are usually readily identifiable. Indeed, the only instance the agency cited to support the cost/benefit analysis of the Proposed Rule concerned an adulterated batch of L-tryptophan known to be limited in quantity and mis-manufactured by a Japanese firm. Proposed Rule at 12,244; see also Exhibit 1 at 2.

In short, the overwhelmingly common characteristic of those who sell dietary supplements is that they sell substances that, among all forms of ingestibles, are the least likely to cause lethality. In an environment of that kind, prior restraints, such as those in the Proposed Rule, are the least defensible. That is because they impose economic

hardship on every company in the industry when only an extreme minority, readily identifiable, is responsible for harms.[17] In other words, prior restraints, such as those in the Proposed Rule, punish through imposition of economic hardship on all in the industry for the sake of guarding against the wrongdoing of a few. Moreover, prior restraints, such as those in the Proposed Rule, operate on the erroneous premise that they will be effective in ridding the market entirely of adulteration. Good actors in the market who now produce products safely by non-cGMP methods may be counted upon to do so with intentional reliance on the cGMPs; bad actors, however, who presently violate the law purposefully (such as those who knowingly spike supplements with drugs or knowingly misbrand them) will likely be undeterred by additional laws against the same wrongful acts. In short, the cGMPs—regardless of their composition—are unlikely to improve significantly the relative level of safety that currently exists in a remarkably safe market.

1. FDA Should Issue Certificates of cGMP Compliance to Subjects Found to Comply with the cGMPs, Thereby Creating a Free Market Incentive for Compliance

The Proposed Rule relies heavily on the threat of sanction to coerce and cajole the regulated class into compliance with the cGMPs. That approach unnecessarily creates a hostile, antagonistic relationship between regulators and the regulated, undermining the goal of constructive cooperation that is essential to maximum implementation of the cGMPs.

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[17] A perverse effect of the Proposed Rule may be to increase the risk of injury from the mis-manufacture of dietary supplements. To the extent that the proposed rule and its enforcement create widespread increased costs it may cause firms to move their manufacturing to certain off shore locations where hygienic practices may be more lax. Off shore facilities are difficult, if not impossible, for FDA to regulate. Such an exodus would diminish FDA's jurisdiction over the industry and may result in the production of more adulterated products than were the firms to remain in countries, such as the U.S., where good hygienic practices are commonplace.

A better approach would be to create, wherever possible, market incentives for improvements in safety. The market already creates such powerful incentives due to consumer discrimination among products, the force of branding, and the potential for lawsuits. FDA can add to the positive market forces by issuing certificates of cGMP compliance to all firms that have passed an FDA cGMP inspection without a cGMP rule violation. FDA should permit those certificates to be placed on labels and in labeling, to alert the public of the fact that the firm in question has passed cGMP inspection. The certificate could remain valid for a term of years or until cGMP noncompliance is established, whichever occurs first.

A certificate program will enable consumers to discriminate among firms in the market based on proof of quality assurance and will encourage firms to achieve those levels of quality assurance to avoid a financial penalty as consumers move toward certified products. There is no substitute for that kind of approach because it brings the value of market force into the equation, creating a maximum market incentive for rule compliance. It also helps diminish the adverse economic effects on a firm from bringing about internal reforms to achieve compliance. The firm that makes such expenditures may expect to recoup at least some of them from increased demand generated by public perception of cGMP compliance by the firm.

2. FDA Should Distinguish cGMP Violations that Present a Significant or Unreasonable Risk of Illness or Injury from Those that Do Not and Limit Enforcement Action to the Former and Request Letters to the Latter

As explained above, the FDCA places the burden of proof on FDA to establish the presence of a dietary supplement or dietary ingredient that "presents a significant or unreasonable risk of illness or injury," 21 U.S.C. § 342(f)(1)(A), precluding FDA from

taking action against a product unless it proves the existence of such a risk. Unless enforcement of the Proposed Rule is limited to such circumstances it will violate 21 U.S.C. § 342(f)(1)(A). Accordingly, the Proposed Rule must be amended to distinguish between rule violations that do present such a risk and those that do not, limiting to the former enforcement action (and "demand" letters as per the discussion supra) and relying in the latter case on recommendations to achieve compliance (and "request" letters as per the discussion supra). Adherence to that approach should alleviate substantially unnecessary financial burdens and lessen the anticompetitive effects of the Proposed Rule.

3. Permitting a 24 Month Period for Voluntary Compliance before the Adopted Rule Is Enforced Would Alleviate Some of the Rule's Financial Burdens and Anticompetitive Effects

In addition to the reform in 3(a) above, the Joint Commenters recommend that FDA make the effective date of the adopted rule 24 months after rule adoption and encourage, during that 24 month period, manufacturers, packagers, and holders to enter a program of voluntary inspection and compliance, thereby lessening the economic impact of the rule by affording more time to achieve compliance. Under this program, companies could invite FDA inspection (without risk of penalty for cGMP violations found) to determine the extent to which compliance with the cGMPs can be achieved in any particular case. FDA, in turn, would apprise the companies of cGMP noncompliance. The company in question would then have a voluntary option to correct the problems before implementation of the rule. FDA would then confirm compliance following an investigation of corrective measures taken. FDA should allow the companies in question to inform the public of that confirmation notice until a date certain

or until such future time, if ever, when the agency notifies the company of an act of noncompliance, whichever occurs first. That approach will create a strong incentive for voluntary compliance in advance of the rule's implementation date and will permit companies to spread out over time the costs of compliance, thereby lessening the economic impact.

4. Permitting Case by Case Alternatives to Costly cGMP Rule Requirements Achieve Rule Goals at Lesser Cost and Alleviate Some of the Rule's Financial Burdens and Anticompetitive Effects

As with all broad regulations that carry with them substantial costs, the cGMPs in the Proposed Rule must be applied prudently to avoid wreaking economic havoc for good actors in the market. The best way to avoid such hardships and chaos is to rely on a case by case approach in which the absence of any actual harm to consumers, the presence of hygienic practices in production, and the apparent commitment and willingness of the subject of investigation to maintain and ensure hygienic practices is weighted heavily in its favor and against issuance of an enforcement "demand" instead of a compliance "request" (see discussion above). When a company under investigation has no prior history of selling products that have caused harm to consumers and has an apparently hygienic operation, the presence of individual violations of the cGMPs that do not present a significant or unreasonable risk of illness or injury should invite a negotiated resolution. In such instance, the agency should refrain from "demands" and rely on "requests." It should not insist on any specific remedial measure but invite the subject to explain economic alternatives to any remedial measure requested.[18] Wherever possible, those

[18] FDA's specification of precise methods for manufacture (e.g. regulation of the kinds of equipment, the placement of equipment, the structure of the physical plant, and the existence and location of hand-washing facilities and bathrooms) are design standards. As explained in Dr. Rubin's report (Exhibit 1), FDA would do well to rely on performance standards rather than design standards in the cGMPs. Performance

economic alternatives should be permitted and on a timetable that does not create economic hardship for the subject of investigation. This flexible regulatory approach is best suited for the dietary supplement market in light of its history of extraordinary safety, in light of the overwhelming predominance (88.9%) of firms having annual gross incomes of $5 million or less, and in light of the fact that other statutory tools exist to permit FDA to take rapid and decisive action against a party that intentionally or negligently creates a significant or unreasonable risk of illness or injury to the public. See, e.g., 21 U.S.C. §§ 333, 334, 335a and 18 U.S.C. § 3571. The Joint Commenters respectfully request that FDA adopt the foregoing flexible regulatory approach to help alleviate the financial burdens and anticompetitive effects of the Proposed Rule.

5. Adopting Lengthened Timetables for Compliance Will Reduce Some Cost Burdens and Reduce the Rule's Anticompetitive Effects

In all instances where a "request" is appropriate, rather than a "demand," as explained above (i.e., whenever FDA does not have evidence that a dietary supplement or dietary ingredient "presents a significant or unreasonable risk of illness or injury,") FDA should confer with the subject of cGMP investigation to avoid adoption of a timetable for compliance that unnecessarily creates economic hardship for the subject. Instead, it should rely on liberal timetables of six months or more with periodic updates as an alternative to insistence on immediate compliance in the absence of a real and present danger to public health.

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standards mandate the outcome that must be achieved, but allow the regulated firm the option of choosing the methods for achieving that outcome. That ensures maximum flexibility and reduces regulatory costs substantially. It is generally agreed that where possible performance standards are preferable since they allow the regulated firm more discretionary authority to achieve the desired outcome at lower costs. They also avoid on of the essential problems of design standards, retardation of innovative means to improve safety. If regulated firms perceive design standards as a safe harbor from adverse regulatory scrutiny, they will rely on them even if that means forgoing innovations that would provide the public greater safety. By contrast, performance standards allow the regulated firm to innovate in ways that will improve safety without fear of adverse regulatory scrutiny.

V. CONCLUSION

For the foregoing reasons, the Joint Commenters respectfully request that the FDA modify the Proposed Rule as requested above. Doing so will eliminate present violations of the applicable provisions of the Food Drug and Cosmetic Act, the Data Quality Act, the Small Business Regulatory Enforcement Act, the Administrative Procedure Act, and the Due Process component of the Fifth Amendment, will lessen the adverse economic impact of the Proposed Rule, and will eliminate significant anti-competitive effects of the Proposed Rule.

Respectfully submitted,

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