BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CITIZEN PETITION

BY THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

FOR REGULATIONS REQUIRING

ADVERSE EXPERIENCE REPORTING FOR DIETARY SUPPLEMENTS

March 20, 2003

The American Herbal Products Association ("AHPA") is the national trade association and voice of the herbal products industry, comprised of companies doing business as growers, processors, manufacturers, and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs. AHPA submits this petition pursuant to 21 CFR §§ 10.25 and 10.30 to request the Commissioner of Food and Drugs to promulgate regulations mandating adverse experience reporting for dietary supplements by manufacturers, packers and distributors of dietary supplement products.

At its October 2, 2002 meeting, the AHPA Board of Trustees determined that AHPA should petition the Food and Drug Administration ("FDA") to promulgate regulations requiring that reports of serious adverse experiences associated with dietary supplements that come to the attention of manufacturers be reported to FDA. There has not previously been a commonly accepted definition of serious adverse experience for dietary supplements. In this proposal, AHPA adopts with minor modifications the definition of and the process for reporting serious adverse experience for prescription drugs that is set forth at 21 C.F.R. § 310.305.

The Dietary Supplement Health and Education Act ("DSHEA") recognized that "dietary supplements are safe within a broad range of intake, and safety problems with dietary supplements are relatively rare" (DSHEA Sec. 2 (14)). And these products are used safely by millions of consumers on a daily basis. Nonetheless, a comprehensive system to document and collect experiences reported by consumers or health care professionals and to identify potential issues of concern accurately and promptly would be in the public interest and also serve to inform regulators, health care professionals,

consumers and the dietary supplement industry regarding the nature of the experiences reported to companies about their products.

Many dietary supplement manufacturers have systems in place to collect and address consumer reports regarding experiences with products that come to the company's attention. Those systems are internal and proprietary to each company and there is presently no single place where the experiences of each company are collected and assessed. Collection of such information in one place serves the salutary purpose of aggregating information that may not appear meaningful when addressed at one company. That information can then be assessed to determine if adverse experience reports constitute signals with respect to potential issues with products or their ingredients. Similarly, a paucity of experiences associated with dietary supplements will have more meaning in the context of a mandatory system for reporting serious adverse experiences.

In the past, AHPA has sought to determine whether a private sector adverse experience reporting system for dietary supplements would provide useful information for assessment. AHPA has now chosen to petition the FDA to establish an adverse event experience reporting system by regulation and to provide the associated protections of 21 CFR §20.63(f) to information submitted to the FDA, the same protections to such information that are now provided to pharmaceutical and medical device manufacturers, i.e., that the names and identifying information of adverse event reporters not be disclosed by FDA or by any company.

AHPA has been active in communicating concerns about the dietary supplement adverse event reporting system (SN/AEMS) that was recently abandoned by FDA. For

example, on February 11, 1998, AHPA submitted a letter to Robert Lake and to Dr. Elizabeth Yetley to discuss the imminent placement of the SN/AEMS on FDA's website. Included in this letter was AHPA's expressed concern that manufacturers' access to information posted on the SN/AEMS website about their products be made readily available and AHPA provided specific suggestions as to how this issue could be addressed. In addition, AHPA addressed a letter to Daniel Troy and to Dr. Christine Taylor on March 28, 2002, to request that certain reports be excluded from kava entries on the SN/AEMS site since FDA had information that the product that was the subject of these certain reports did not contain kava, and in fact contained an illegal drug.

To the best of AHPA's institutional memory, the only formal response AHPA received to these communications was to the last mentioned. On August 29, 2002, the date of an FDA telephone conference announcing the termination of the SN/AEMS and the introduction of a new system (the CFSAN Adverse Event Reporting System, or CAERS), Dr. Taylor acknowledged receipt of AHPA's correspondence and informed AHPA that the Center had decided to remove the SN/AEMS website.

AHPA is concerned about FDA's practice in the past to make summary adverse event reports available on its website for dietary supplements but not for other regulated products. For example such summary reports are not made available by FDA for prescription drugs. And there is no system at all for adverse experience reporting for nonprescription drugs that are not new drugs. With respect to cosmetics, reports are now available to the public only on an annual basis. AHPA does not oppose the public availability of information regarding dietary supplement adverse experience reports. AHPA does object, however, to a system that provides prompt access to information

regarding dietary supplements while such information regarding other regulated products is far less accessible.

I. Action Requested

AHPA requests FDA propose and publish in the Federal Register for comment, a regulation requiring reporting of serious adverse experiences associated with dietary supplement products as follows:

> xxx.xxx **Records and reports concerning serious adverse experiences on marketed dietary supplement products.**
>
> (a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed dietary supplement products to establish and maintain records and make reports to FDA of all serious adverse dietary supplement experiences received or otherwise obtained that are associated with the use of their products. Any person subject to the reporting requirements of paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of serious adverse dietary supplement experiences to FDA.
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> (b) *Definitions.* The following definitions of terms apply to this section:
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> *Adverse dietary supplement experience.* Any adverse event associated with the use of a dietary supplement in humans, whether or not considered dietary supplement related, including the following: An adverse event occurring in the course of the use of a dietary supplement product; an adverse event occurring from dietary supplement use, whether accidental or intentional; and an adverse event occurring from dietary supplement abuse.
>
> *Disability.* A substantial disruption of a person's ability to conduct normal life functions.
>
> *Life-threatening adverse dietary supplement experience.* Any adverse dietary supplement experience that places the user, in the view of the initial reporter, at *immediate* risk of death from the adverse dietary supplement experience as it occurred, i.e., it does not include an adverse dietary

supplement experience that, had it occurred in a more severe form, might have caused death.

Serious adverse dietary supplement experience. Any adverse dietary supplement experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse dietary supplement experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse dietary supplement experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

(c) *Reporting requirements.* Each person identified in paragraph (c)(1) of this section shall report to FDA serious adverse dietary supplement experience information as described in this section and shall submit one copy of each report to _____.

(1) *30-day reports.* Any person whose name appears on the label of a marketed dietary supplement product as its manufacturer, packer, or distributor shall report to FDA, in the form provided by FDA for such reporting, each serious adverse dietary supplement experience received or otherwise obtained as soon as possible, but in no case later than 30 calendar days of initial receipt of the information by the person whose name appears on the label. Each report shall be accompanied by a copy of the current labeling for the dietary supplement product.

(2) *30-day report follow-up.* Each person identified in paragraph (c)(1) of this section shall promptly investigate all serious adverse dietary supplement experiences that are the subject of these 30-day reports and shall submit follow-up reports within 30 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. 30-day reports and follow-ups to them shall be submitted under separate cover.

(3) *Submission of reports.* To avoid unnecessary duplication in the submission of, and follow-up to, reports required in this section, a packer's or distributor's obligations may be met by submission of all reports of serious adverse dietary supplement experiences to the manufacturer of the dietary supplement product. If a packer or distributor elects to submit serious adverse dietary supplement experience reports to the manufacturer rather than to FDA, it shall submit each report to the manufacturer within 5 calendar days of its receipt by the packer or distributor, and the manufacturer shall then comply with the requirements of this section even if its name does not appear on the label of the dietary supplement product. Under this circumstance, the packer or distributor shall maintain a record of this action which shall include:

(i) A copy of each serious adverse dietary supplement experience report;

(ii) The date the report was received by the packer or distributor;

(iii) The date the report was submitted to the manufacturer; and

(iv) The name and address of the manufacturer.

(4) Each report submitted to FDA under this section shall bear prominent identification as to its contents, i.e., "30-day report," or "30-day report-follow-up."

(5) A person identified in paragraph (c)(1) of this section is not required to resubmit to FDA serious dietary supplement adverse experience reports forwarded to that person by FDA; however, the person must submit all follow-up information on such reports to FDA.

(d) *Reporting form.*

(1) Except as provided in paragraph (d)(3) of this section, each person identified in paragraph (c)(1) of this section shall submit each report of a serious adverse dietary supplement experience on an FDA Form.

(2) Each completed FDA Form should pertain only to one individual subject.

(3) Ten copies or fewer of FDA Form ___ and/or a copy of the instructions for completing the form may be obtained from the Office of [to be determined]. More than 10 copies of the form may be obtained by writing to the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785. Such forms may also be found on FDA's website at www.fda.gov.

(e) *Subject privacy.* Manufacturers, packers, and distributors should not include in reports under this section the names and addresses of individual subjects; instead, the manufacturer, packer, and distributor should assign a unique code number to each report, preferably not more than eight characters in length. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received. Names of subjects, individual reporters, health care professionals, hospitals, and geographical identifiers in adverse dietary supplement experience reports are not releasable to the public under FDA's public information regulations in Part 20 of this chapter.

(f) *Recordkeeping.*

(1) Each manufacturer, packer, and distributor shall maintain for a period of 10 years records of all serious adverse dietary supplement experiences required under this section to be reported, including raw data and any correspondence relating to the serious adverse dietary supplement experiences, and the records required to be maintained under paragraph (c)(4) of this section. Such records may not be used in any criminal prosecution of any individual.

(2) Manufacturers and packers may retain the records required in paragraph (f)(1) of this section as part of its complaint files maintained under dietary supplement cGMPs.

(3) Manufacturers, packers, and distributors shall permit any authorized FDA employee, at all reasonable times, to have access to and copy and verify the records established and maintained under this section.

> (g) *Disclaimer and No Admission.* In accordance with 21 U.S.C. Sec. 379(v), a report or information submitted by a manufacturer, packer, or distributor under this section (and any release by FDA of that report or information) does not reflect a conclusion by the manufacturer, packer, or distributor, or by FDA, that the report or information constitutes an admission that the dietary supplement caused or contributed to an adverse effect. The manufacturer, packer, or distributor need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the dietary supplement caused or contributed to an adverse effect.

In addition, 21 CFR Sec. 20.63 should be amended with the information set forth in bold:

> (h) The names and any information that would identify the voluntary reporter or any other person associated with an adverse event involving a **dietary supplement,** human drug, biologic, or medical device product shall not be disclosed by the Food and Drug Administration or by a manufacturer in possession of such reports in response to a request, demand, or order. Information that would identify the voluntary reporter or persons identified in the report includes, but is not limited to, the name, address, institution, or any other information that would lead to the identities of the reporter or persons identified in a report. This provision does not affect disclosure of the identities of reporters required by a Federal statute or regulation to make adverse event reports. Disclosure of the identities of such reporters is governed by the applicable Federal statutes and regulations.

II. Statement of Grounds -- Post-Marketing Dietary Supplement Surveillance and AER Systems

The subject of adverse experience reporting for dietary supplements has been discussed in various forums since the passage of the Dietary Supplement Health and Education Act of 1994 ("DSHEA"). These discussions are set forth below. In summary, these discussions demonstrate that the time has come for a mandatory adverse event reporting system for dietary supplements.

A. In the draft of regulations for current Good Manufacturing Practices for dietary supplements drafted and submitted by AHPA and other trade associations to the Food and Drug Administration November 20, 1995 and published by FDA February 6, 1997 (62 Fed. Reg. 5699), the section on Warehousing, Distribution and Post-Distribution Procedures provided for complaint handling as follows:

> d) Complaint files. (1) Written procedures describing the handling of all written and oral complaints regarding a dietary product shall be established and followed. Such procedures shall include provisions for review by the quality control unit of any complaint involving the possible failure of a product to meet any of its specifications and, for such products, a determination as to the need for an investigation. (2) A written record of each complaint shall be maintained, until at least 1 year after the expiration date of the product, or 1 year after the date that the complaint was received, whichever is longer. (3) The written record shall include, where known: The name and description of the product, lot number, name of complainant, nature of complaint, and reply to complainant, if any. (4) Where an investigation is conducted, the written record shall include the findings of the investigation and follow-up action taken.

These draft regulations demonstrated that the dietary supplement industry generally was fully prepared to implement mandatory complaint handling procedures.

B. The National Nutritional Foods Association (NNFA) has adopted with minor changes the cGMPs proposed by industry in 1995. NNFA members may have their facilities inspected by third parties and receive cGMP certification under NNFA Good Manufacturing Practice Certification Program. Since NNFA instituted this program in June 1999, 40 NNFA manufacturers have received certification. This means that each of these companies have presumably had their complaint handling procedures audited.

C. With respect to the 1995 cGMP proposal by the dietary supplement industry for complaint handling, FDA articulated concerns regarding adverse experience reporting by asking for specific comment on this subject when it published that draft for comment in 1997. 62 Fed. Reg. 5700 (Feb. 6, 1997). The FDA cGMP regulations for the manufacture of dietary supplements proposed March 13, 2003 (68 Fed. Reg. 12158) require in Section 111.95 that consumer reports of adverse events be evaluated by the quality control department. The mandatory reporting system for serious adverse events proposed in this petition by AHPA complements this process by requiring that serious adverse experiences associated with dietary supplements be reported to FDA.

D. Adverse experience reporting with respect to dietary supplements has been in several by independent commissions and others. These include the Commission on Dietary Supplement Labels in its November 1997 report, the FDA response to that report, the July 1999 Report entitled *DIETARY SUPPLEMENTS - Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*, by the General Accounting Office, the Office of the Inspector General of the Department of Health and Human Services report entitled *Adverse Event Reporting for Dietary Supplements* on February 12, 2001 and the report of The White House Commission on Complementary and Alternative Medicine Policy.

Against this background, it is clear that there is a public policy justification for the reporting by manufacturers of serious adverse experiences for dietary supplements.

III. Statement of Grounds Legal Basis for Mandatory Adverse Event Reporting for Dietary Supplements.

In October 8, 2002 testimony before the Senate Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia, Deputy Commissioner Lester Crawford stated that "the recommendation to require adverse event reporting for dietary supplements requires a change in the current law." In a November 22, 2002 letter to AHPA, Mr. Crawford repeated that conclusion. As will appear below, AHPA believes that FDA has ample legal authority to require adverse event under existing law. AHPA encourages FDA to reexamine its position.

In 1994, DSHEA was enacted into law. DSHEA is a public health regulatory statute that establishes a comprehensive scheme for the regulation of dietary supplements. The use of new dietary ingredients must be reported to the FDA in advance of their marketing. Statements of nutritional support for dietary supplements (structure-function claims) must be reported to FDA within thirty days of their first use. Dietary supplements are deemed to be adulterated if they present a significant or unreasonable risk of illness or injury and cannot be labeled for safe use or if they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury. The Secretary of Health and Human Services may also declare an imminent hazard with respect to a dietary supplement product.

This law also specifically gave FDA the authority to promulgate current Good Manufacturing Practice regulations for dietary supplements. As set forth above, AHPA and other dietary supplement trade associations proposed to FDA that such cGMP

regulations require companies have complaint handling and follow-up procedures. Information made available to the FDA through the complaint files of a company may establish whether a dietary supplement is adulterated or whether its labeling is false or misleading. When such circumstances are found, they are commonly remedied through inspectional findings, warning letters, labeling revisions or voluntary recalls. Absent a voluntary recall or change in labeling, the FDA may recommend that the Department of Justice initiate seizure actions or seek injunctive relief. Furthermore, the information may justify FDA□s dissemination of public information, which it is entitled to do under the law and which has become the means most utilized with respect to safety issues regarding dietary supplements.

The Federal Food, Drug, and Cosmetic Act ("FFDCA"), which DSHEA amends, is one of this country's oldest public health protection laws. Section 701(a) of the FFDCA authorizes FDA to promulgate regulations for the efficient enforcement of the act and this section has been used to promulgate cGMP for foods as well as HACCP requirements for certain classes of foods. AHPA believes that the FDA should conclude that the DSHEA enforcement and FFDCA enforcement and publicity provisions of the act could be more efficiently enforced under the reporting requirements proposed in this petition. See Adverse Drug Experience Reporting Requirements for Marketed Prescription Drugs Without Approved New Drug or Abbreviated New Drug Applications (proposed rule, 50 Fed Reg. 11478 (Mar. 21, 1985), final rule 51 Fed. Reg. 24476 (July 3, 1986)) wherein FDA reached a similar conclusion for prescription drugs. The submission of adverse experience reports would enable FDA to determine at the earliest possible time whether to request a dietary supplement manufacturer or

distributor to recall a product, change its labeling, or to request that the Department of Justice take seizure or injunctive action or that the Secretary declare an imminent hazard. Moreover, such information would allow FDA to ascertain how best to use its scarce enforcement resources.

As demonstrated above, FDA has utilized its rulemaking power creatively to mandate adverse experience reporting for drugs that are not new drugs. 21 C.F.R. Sec. 310.305. Similarly, FDA has used its rulemaking power creatively to require safety substantiation labeling for cosmetics, 21 C.F.R. Sec. 740.11, to impose important requirements for low-acid foods in hermetically sealed containers, 21 C.F.R. Part 113, and for cGMP for bottling of bottled drinking water. 21 C.F.R. Part 129. There is no principled reason why this rulemaking authority should not be applied creatively as petitioned for herein to mandate a serious adverse experience reporting system for dietary supplements.

V. Environmental Impact

Neither an environmental assessment nor an environmental impact statement is required where the action requested of the agency action is categorically excluded pursuant to 21 C.F.R. Sec. 25.30(h) in that it is concerned with issuance of procedural or administrative regulations and guidelines.

VI. Economic Impact

According to 21 C.F.R. Sec. 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of the petition.

VII. Certification

AHPA certifies that to the best of its knowledge and belief, that this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

CONCLUSION

On the basis of the foregoing, AHPA respectfully requests that its petition be granted and that FDA publish proposed regulations for mandatory serious adverse experience reporting for dietary supplements.

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March 20, 2003

Hand Delivered

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Dear Sir/Madam:

Enclosed herewith for filing are an original and three copies of a Citizen Petition by the American Herbal Products Association for Regulations Requiring Adverse Experience Reporting for Dietary Supplements.

Thank you for your assistance.

Sincerely,

Anthony L. Young

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Enclosures