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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

September 17, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 98N-0359: 2002 Program Priorities for Dietary Supplements in the Center for Food Safety and Applied Nutrition

Dear Madam or Sir:

The Consumer Healthcare Products Association (CHPA)[1] submits these comments in response to FDA's notice in the *Federal Register* of July 18, 2001 concerning Program Priorities in the Center for Food Safety and Applied Nutrition (CFSAN).

CHPA strongly supports CFSAN's outreach to stakeholders in developing its yearly program of work, as well as the quarterly updates CFSAN issues in relation to progress made on its program of work and any re-prioritizations that may be necessary. Overall, CHPA encourages further development of the regulatory environment for dietary supplements, consistent with the 1994 Dietary Supplement Health Education Act

[1] CHPA is a 120-year-old trade organization representing the manufacturers and distributors of national and store brand dietary supplements and nonprescription medicines. CHPA's membership includes over 200 companies involved in the manufacture and distribution of these self-care products and their affiliated services (e.g., raw material suppliers, research testing companies, contract manufacturing companies, advertising agencies, etc.).

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(DSHEA) and FDA's ample enforcement authority under the Food Drug & Cosmetic (FDC) Act.

CHPA submitted comments on August 25, 2000 in relation to CFSAN's Program Priorities for 2001. At that time, CHPA agreed with the strategic approach taken by CFSAN to ask the question, "*where do we do the most good for consumers?*" and urged FDA to place safety, including enforcement of ingredient safety issues and labeling, issuance of the GMPs, and development of an effective AER management system within CFSAN. Among other things, CHPA also urged action on its pending Citizen Petitions relating to St. John's wort, pregnancy/nursing labeling, and structure/function final rule, as these petitions bear directly on safe and effective use of dietary supplements by consumers. CHPA also suggested the creation of an AER Ad Hoc Working Group that would provide recommendations to FDA on how they could reengineer the current AER system or create a new system for dietary supplements.

Over 2000-2001 some progress has been made in the area of safety, and FDA has successfully exercised its authority under the FD&C Act to remove certain dietary ingredients from the marketplace (e.g., comfrey). However, notwithstanding such activities, we believe that we are still a long way from realizing a comprehensive safety system for dietary supplements that encompasses all the requisite elements, including:

- a framework for evaluating the science of dietary supplements, which is now under development by the National Academy of Sciences Institute of Medicine (IOM);
- a well-developed adverse experience monitoring system with adequate staffing for electronic-based collection activities, competent medical reviews, training, etc., which has yet to be fully developed;
- a framework for potential public health interventions by FDA, based on CFSAN-initiated safety reviews (e.g., labeling, product withdrawal, education), and this

includes an articulated labeling policy that has yet to be defined in the context of "failure to reveal a material fact" [i.e., 201(n) of the Act];

- a final regulation on Good Manufacturing Practices (GMPs) for dietary supplements, that has languished inexplicably within the Administration;
- a reasonable enforcement program consistent with DSHEA that includes an appropriate level of inspections, which are dependent on issuance of GMPs and adequate appropriations for field activities;
- a more efficient working relationship with the Federal Trade Commission (FTC) that ensures a more consistent development of label statements, whether applied in an FDA rulemaking or in a punitive manner specific to an FTC enforcement action.

As noted, certain elements of a comprehensive safety system for dietary supplements are under development as "priority A" items, including IOM's activities to (1) develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues, (2) describe a process for developing a system of scientific reviews with specifications for evaluating the safety of dietary supplement ingredients, and (3) develop at least six scientific reviews as prototypes for the system. Further, issuance of proposed GMPs appear to be out of CFSAN's immediate control, given that they are at the Office of Management and Budget (OMB). Nonetheless, the safety system outlined above requires "priority A" attention by CFSAN, because this is where CFSAN can do the most good for consumers as it relates to dietary supplements.

CHPA's Detailed Comments follow on the next page.

A summary itemization of CHPA's specific recommendations that are elaborated in the Detailed Comments can be found in the Conclusions section.

CHPA's Detailed Comments and Recommendations

1. **Good Manufacturing Practices**: GMP regulations for dietary supplements are important for the following reasons: a) differing needs exist in the manufacture of dietary supplements vs. foods, specifically related to in-process controls, laboratory controls and quality control/quality assurance (QA/QC) specifications, and b) there are at least three sets of GMPs now in use for dietary supplements, specifically, the food GMPs, the dietary supplement industry-proposed GMPs, and GMPs used under the voluntary program of the National Nutritional Foods Association. GMP regulations would lead to uniformity in how manufacturing processes are evaluated, thus raising the level of quality of products in the market place. In addition, GMPs will raise the level of awareness among suppliers, manufacturers and distributors regarding the need for quality operations.

   On February 6, 1997, the Agency published an advanced notice of proposed rulemaking in the *Federal Register*. It has been over four years since the publication of this document. Although the Agency has indicated in several public forums that it has placed publication of a proposed rule on high priority, its appearance in the *Federal Register* appears to be a moving target date for the Agency. Without GMPs specific to dietary supplements, it is difficult to demonstrate to the public that the FDA is serious about consumer safety and its obligation to regulate dietary supplements. As a "priority A" activity, CFSAN should actively seek ways within the Administration to obtain publication of the GMPs. It is simply not credible for an agency of the Administration to say that a needed regulation is "out of its hands."

   Furthermore, CHPA has written to CFSAN requesting an opportunity to work with CFSAN to develop at least two industry-wide briefing sessions for the proposed GMPs when they are issued. CHPA reiterates its request that such briefings be given a "priority A" rating in the 2001 Program Priorities. CHPA stands ready to help facilitate these sessions.

2. **AERs**: CHPA asks FDA to create an AER Ad Hoc Working Group, which would provide recommendations to FDA how they could reengineer the current or create a new AER system for dietary supplements. An effective AER system for dietary supplements is important to ensure that safe products continue to remain in the marketplace. A science-based discussion on realistic approaches to AER management, which includes topics such as the analysis of AER's and science-based approach to AER filtering, is important. Therefore, CHPA recommends that CFSAN create an Ad Hoc AER Working Group. This group should include representation from industry, and provide a review of and recommendations for changes to FDA's existing AER system to better serve the needs of consumers, professionals, industry and the agency.

   While the OIG issued a number of recommendations pertinent to the development of an adequate AER system within CFSAN, the report by its own admission was flawed in that it did not evaluate CFSAN's current operating procedures (see attached comments by CHPA on this matter as Attachment A). Hence, CHPA specifically does not recommend that CFSAN use the OIG report as a basis for developing a comprehensive AER system.

3. **Needed Policy Framework for Labeling:** Under DSHEA, a dietary supplement is adulterated if it or one of its ingredients presents "a significant or unreasonable risk of illness or injury" when used as directed on the label, or under normal conditions of use. It is the dietary supplement manufacturer's responsibility to ensure that its products are safe, effective, and properly labeled, consistent with DSHEA and implementing regulations. This responsibility includes ensuring dietary supplement labels bear facts that are material in light of consequences that may result from use of the product or representations made about it.[2] Thus, CFSAN's actions on labeling

[2] CFSAN's policy relating to material fact labeling has been put forth in part in the preamble to the structure/function final rule as follows: "FDA agrees that it is important to inform consumers about potential adverse effects or drug interactions for specific dietary supplement ingredients. In fact, dietary supplement labeling, like the labeling of other FDA-regulated products, is required to include all facts that are material in light of consequences that may result from use of the product or representations made about it (sections

have encompassed issuance of final regulations for structure/function claims, health claims, defining boundaries (e.g., regarding OTC drug/dietary supplement combinations) and certain safety alerts (e.g., St. John's wort and drug interactions). However, CFSAN has taken no specific steps to help manufacturers understand what safety information represents a material fact finding or to provide guidance to manufacturers as to what label language relating to a safety issue meets the requirement to reveal a material fact.

This matter should receive CFSAN's immediate attention, yet we have been told that resource limitations within CFSAN prevent this from happening. Over the past year and a half, we have submitted three Citizen Petitions requesting adoption of specific safety-related labeling information for selected dietary supplements.[3] We understand that the St. John's wort and ephedra Citizen Petitions represent a low priority for CFSAN, that the Center for Drug Evaluation and Research not CFSAN has the lead for pregnancy/nursing labeling, and that issuance of a guidance or regulation on the matter of revealing material facts on dietary supplement labels is a secondary priority for CFSAN (see 2001 CFSAN Priority B list of dietary supplements).

Without a defined publicly articulated policy by CFSAN, manufacturers do not have a level playing field, with certain companies understanding better their responsibilities under DSHEA than others. It is the reason CHPA stepped forward with voluntary labeling programs. Further, the States and sister federal agencies typically step in where the Food and Drug Administration leaves a void (e.g., recent Texas and California actions on ephedra labeling and the June 2001 label enforcement actions by the Federal Trade Commission relating to St. John's wort, pregnancy/nursing labeling, and ephedra). These actions have the potential to create

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403(a)(1) and 201(n) of the act). This provision is not intended in any way to preclude truthful adverse event or drug interaction information from appearing in a dietary supplement's labeling." [Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule; *65 Federal Register* 999-1050 (1/6/2000)]

[3] CHPA's Citizen Petitions requested warning statements relating to use of dietary supplements by pregnant or nursing women (May 4, 2000), potential prescription drug interactions (submitted June 20, 2000), and ephedra (January 26, 2001).

inconsistent labeling information across product categories, to the detriment of the consumer.

Clearly the matter of defining a dietary supplement labeling policy should be placed in the "priority A" list for immediate attention and action by CFSAN. The timing is right to begin this activity in view of CFSAN's sponsored project with the Institute of Medicine (IOM) to create a scientific framework for safety evaluations of dietary supplements and IOM's review of six supplements. When that work is completed, CFSAN may be faced with certain "findings of material fact" relating to safety on those ingredients that are chosen for review. Without a clear labeling policy in place, the agency will be caught flat-footed.

4. **CFSAN/FTC Interactions on Labeling Issues:** CHPA supports effective enforcement consistent with the scope and intent of DSHEA, as well as effective communication with consumers through labels. Indeed, a CHPA Board policy supports the principles set forth in FTC's "Dietary Supplements: Advertising Guide for Industry."

Our concern, however, relates to the importance of striking the right balance between effective enforcement and consistent labeling for dietary supplements. This is particularly important where two different agencies might engage in development of label requirements for dietary supplements for
similar but ultimately different reasons: i.e., FDA in terms of defining a consistent science-based standard across the industry; FTC in terms of remedial labeling to correct outlandish claims of safety.

In FTC's "Dietary Supplements: An Advertising Guide for Industry," it states that:

"The Federal Trade Commission (FTC) and the Food and Drug Administration (FDA) work together under a long-standing liaison agreement governing the division of responsibilities between the two agencies. As applied to dietary supplements, the FDA has primary responsibility for claims on product labeling, including packaging,

inserts, and other promotional materials distributed at the point of sale. The FTC has primary responsibility for claims in advertising, including print and broadcast ads, infomercials, catalogs, and similar direct marketing materials. Marketing on the Internet is subject to regulation in the same fashion as promotions through any other media. Because of their shared jurisdiction, the two agencies work closely to ensure that their enforcement efforts are consistent to the fullest extent feasible."[4]

In the case of recent actions by FTC against companies making unsubstantiated safety claims[5], the enforcement action by FTC, while intended to be limited to the respondents to "fence in" their future actions, potentially raises several important concerns, including:

- A concern that the two agencies may have a different standard for dietary supplement labeling;
- A concern that FTC's enforcement actions may be misread by state and local enforcers as the federal requirements for dietary supplement labels, although there has been no notice and comment period for rulemaking for such labeling, this is contrary to due process;
- A concern that FTC's enforcement actions could establish label requirements differ from those used by industry or required by individual states, could create unneeded inconsistency or lack of uniformity in current dietary supplement warning practices and thus lead to consumer confusion;
- A concern that FTC's actions, which might be followed by FDA actions on similar products that were not subject to the FTC enforcement action, would lead to multiple unneeded label changes as responsible companies seek conformity with FTC enforcement actions (even if the action does not apply to their labels) and subsequent FDA regulations.

Therefore, CHPA urges development by CFSAN and FTC of a publicly-articulated consistent approach, with one agency (FDA) responsible for defining the

[4] http://www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm

[5] Federal Trade Commissioner News Release: "Operation Cure.All" Wages New Battle in Ongoing War Against Internet Health Fraud, June 14, 2001.

overarching policy for DS labeling through a public (stakeholder) process, which would support a case-by-case enforcement policy based on joint FDA/FTC action, where appropriate. This would include an inter-agency agreement between FDA and FTC specifically stating that any enforcement actions generated by label statements would apply specifically to the products stipulated in the enforcement action and not to other products with similar formulations.

5. **Enforcement of Dietary Ingredient Safety Issues:** While FDA has taken action on certain specific safety issues, CHPA believes that there are a cadre of dietary ingredients about which most, if not all, experts agree represent a safety hazard because of their toxicity. Indeed, CHPA and the American Herbal Products Association (AHPA) have voluntary programs pertaining to certain of these toxins including pyrollizidine alkaloids and certain contaminants (see attached list of CHPA voluntary programs for dietary supplements as Attachment B). And, at an open meeting on February 1, 2001, which included representation from the major trade associations, CFSAN and consumer groups, there was general consent that there was likely a core group of toxicants and contaminants for which there would be general agreement that they should not be marketed as or in dietary supplements. CHPA urges CFSAN to continue to take action on known toxicants and contaminants which should not be marketed as or in dietary supplements and publish its findings as a means to further build the safety base of the industry and raise awareness among manufacturers and the public.

   Along these lines, CHPA agrees with ephedra being a "priority B" item, given that further development of IOM's scientific framework for safety evaluations of dietary supplements will undoubtedly be needed before sound policy-based actions, if any, can be taken on this ingredient. Further, CHPA agrees that BSE remain a top priority, given the need for vigilance.

6. **Specific Labeling Issues -- CHPA Citizen Petitions: CHPA** still awaits a response to the St. John's wort and Pregnancy/Nursing label statements, and other citizen

petitions filed by CHPA in 2000, and asks that these be placed as a "priority A" activity along with the other matters relating to labeling outlined above.

The following is a list of petition filing dates:

Citizens Petition	**Date Filed**
St. John's wort: Requests FDA to issue a regulation requiring a label statement on dietary supplements containing St. John's wort.	June 20, 2000
Pregnancy/Nursing: Requests FDA to issue a regulation requiring label statements on certain dietary supplements pertaining to their use in pregnancy and/or when nursing a baby.	May 11, 2000
Ephedra: Requests FDA to issue a regulation adopting the elements of labeling used voluntarily by industry.	October 25, 2000
Structure/Function Final Rule: Petition for Reconsideration and Stay of Action to reverse a decision announced in the preamble to the final structure/function claims rule concerning claims for conventional foods and for dietary supplements having nutritive value.	February 7, 2000
Structure/Function Final Rule: Petition for Stay of Action asking FDA to stay the 30-day compliance date for parts of the final structure/function rule for products ready for launch but not marketed by January 6, 2000.	February 7, 2000

Conclusion

In conclusion, CHPA asks FDA to continue to place safety concerns as its number one priority for dietary supplements in 2002. CHPA urges CFSAN to take a systems approach to safety, as outlined in these comments, and not only continue the "priority A" development of certain related activities that are now underway (e.g., IOM safety review activities), but also reprioritize certain "priority B" activities (e.g., development of a guidance or regulation on "material fact labeling"), and develop certain "new priority A" activities (e.g., action on CHPA Citizen Petitions).

In doing so, the Agency will address the one central question the Agency uses in its priority-setting process (i.e., "*Where do we do the most good for consumers?*") by focusing comprehensively on safety.

Recap of CHPA's Recommendations Made in the Detailed Comments

1. As a "priority A" activity, CFSAN should actively seek ways within the Administration to obtain publication of dietary supplement GMPs. (page 4)

2. CHPA reiterates its request that CFSAN work with CHPA on GMP briefings as s "priority A" item in 2002. (page 4)

3. CHPA asks FDA to create an AER Ad Hoc Working Group, which would provide recommendations to FDA how they could reengineer the current or create a new AER system for dietary supplements. (page 4)

4. For reasons stated in CHPA's comments and Attachment A, CHPA specifically does not recommend that CFSAN use the OIG report as a basis for developing a comprehensive AER system. (page 5)

5. Defining a dietary supplement labeling policy, specifically as it relates to "material fact labeling," should be placed in the "priority A" list for immediate attention and action by CFSAN. (page 7)

6. CHPA urges development by CFSAN and FTC of a publicly-articulated consistent approach, with one agency (FDA) responsible for defining the overarching policy for DS labeling through a public (stakeholder) process, which would support a case-by-case enforcement policy based on joint FDA/FTC action, where appropriate. This would include an inter-agency agreement that the FTC would specifically state that

any label statements and related enforcement actions apply specifically to the products stipulated in the enforcement action and not to other products with similar formulations. (page 8-9)

7. CHPA urges CFSAN to continue to take action on known toxicants and contaminants which should not be marketed as or in dietary supplements and publish its findings as a means to further build the safety base of the industry and raise awareness among manufacturers and the public. (page 10)

8. CHPA agrees with ephedra being a "priority B" item, given that further development of IOM's scientific framework for safety evaluations of dietary supplements will undoubtedly be needed before sound policy-based actions, if any, can be taken on this ingredient. Further, CHPA agrees that BSE remain a top priority, given the need for vigilance. (page 10)

9. CHPA still awaits a response to the St. John's wort and Pregnancy/Nursing label statements, and other citizen petitions filed by CHPA in 2000, and asks that these be placed as a "priority A" activity along with the other matters relating to labeling outlined above. (page 10-11)

Sincerely yours,

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

Leila Saldanha, Ph.D., R.D.
Vice President, Nutritional Sciences

Attachments: A, Letter from CHPA to OIG on AER Reporting for Dietary Supplements
B, CHPA Voluntary Programs for Dietary Supplements

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Producers of Quality Nonprescription Medicines and Dietary Supplements for Self-Care

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

April 4, 2001

Michael F. Mangano
Acting Inspector General
Office of the Inspector General
Department of Health & Human Services
Washington, DC 20201

Dear Mr. Mangano:

Thank you for the opportunity to review and comment on the draft Inspection Report, "Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve" prepared by the Office of the Inspector General (OIG). We recognize the importance of adverse event reporting (AER) systems and have supported better operating procedures for the current AER system in past comments to the agency.[1]

The Consumer Healthcare Products Association (CHPA) is the 120-year-old trade organization representing companies involved in the manufacture, distribution, supply, advertising and research of dietary supplements and nonprescription medicines. We have been intimately involved in commenting on the evolving regulatory frameworks for both the OTC drug and dietary supplement components of the consumer self care industry. In particular, we have had a very significant involvement in both mandatory and non-mandatory AER systems in the dietary supplement and nonprescription drug industries and use this experience to provide you with detailed comments on the draft Inspection Report. However, given your short turn around time for comments, we may have additional comments as we complete our continued review of the Inspection Report.

I. Executive Summary

It is important that the Inspector General know our interest in an adequate AER system for dietary supplements. However, notwithstanding our interest in and support for adequate post-marketing surveillance of dietary supplement products, our extensive experience in this area leaves us with the conclusion that the draft Inspection Report is flawed in its approach, and is therefore of incomplete value in being a credible basis for further development of adequate and reasonable AER management within the Center for Food Safety and Applied Nutrition (CFSAN).

[1] E.g., see CHPA's comments to Docket No. 99N-1174 pertaining to the June 8, 1999 CFSAN Stakeholder Meeting dated June 8, 1999 and August 20, 1999.

The core failing in the findings of the draft Inspection Report is the OIG's admission that "we do not evaluate the internal operating procedures of [CFSAN's] system" (page 8, last sentence). Without a completely adequate audit and evaluation of CFSAN's operating procedures for managing AERs, including CFSAN's scientific capacity to manage and evaluate the existing reports as well as CFSAN's documented procedures manuals and policies for such management, there is little support for recommendations that would result in wholesale changes to the current AER system for the subset of foods known as dietary supplements – particularly, changes that would represent requirements over and above those even required for foods or, for that matter, a very large category of nonprescription drugs.

Indeed, since CFSAN has indicated that it is seriously under-funded to effectively manage the current system, having asked Congress for two years in a row for $2.5 million for operational development of its AER reporting system, it is premature to suggest total revamp of the current system. Rather, it would be more appropriate to determine the adequacy of the system if funding were made available.

We believe the current system can work with adequate funding to improve current operating procedures and functions as well as creation of awareness outreach programs, so that consumers and health professionals are aware of the need for, and methods to, report AERs on dietary supplements, as well as other health-related products.

As a result, CHPA asks that the Inspector General have the draft report re-evaluated before its official publication, so that its conclusions can be appropriately modified to more realistically define workable solutions to the current problems faced by CFSAN in managing AERs. Those solutions do not include a ground-up restructuring of the dietary supplement AER system in CFSAN, but rather a recognition that the current system is workable through refinements, based on increased resources for operational management and on a public education campaign relating to dietary supplements and MedWatch. We therefore recommend refinements of the current capacities of the existing system, which would keep the level of regulatory requirements consistent with those required for conventional foods, including:

1. CFSAN should develop, if it has not already done so recently, detailed operating procedures for the current AER systems.

2. CFSAN should be funded to: (a.) create and operate a state-of-the-art computer system for tracking and compiling AERs reportedly associated with dietary supplement use; (b.) manage FOI requests on AERs on a timely manner and keep the AER website updated (note: "relatedness" conclusions should not appear on the website, for the reasons given below); (c.) develop as a 2001 "A list" priority a regulatory policy framework for requiring label statements on dietary supplements, based on scientific documentation of signals in the AER system.

3. Importantly, mandatory AE reporting, registrations, and labeling requirements for toll free numbers is unnecessary as a means to have an effective safety valve in the form of an operationally-intact AER system within CFSAN, given the reasons set forth below.

(See below for detailed comments.)

II. Detailed Comments

In reassessing the Inspection Report, OIG should seriously consider incorporating the following points.

1. The AER system for dietary supplements is more than just AE reports to MedWatch and is workable with improved funding.

The AER system for consumer products, whether dietary supplements or monograph OTC drugs, is a complex system involving surveillance of the spontaneous reports as well as the published literature, poison control reports, and other information as might come to the attention of FDA, companies and health professionals. As such, the Inspection Report focuses principally on the spontaneous report component of the AER system, leading to a set of conclusions that are not only over-reaching in their specifics but also appear out of context of what is workable and achievable.

Specifically, the AER system for dietary supplements is set up to be potentially both a passive and active surveillance system, not unlike that used for OTC monograph drug ingredients. The OTC component run by CDER has identified numerous post-marketing signals on OTCs that had been marketed for many years with no indication of purported safety concerns (e.g., benzoyl peroxide, water-soluble gum, doxylamine, diphenhydramine etc.). These reports stemmed from either spontaneous AERs or from case reports or case series in the published literature. The OTC AER system has been shown to be quite sensitive to rare adverse events associated with marketed OTC ingredients (e.g., rare neosporin-related allergy), and as needed, wehave stepped forward with Citizen Petitions to seek appropriate scientifically-documented labeling changes.

Similarly, CFSAN's post-marketing surveillance system for dietary supplements has picked up signals for potential problems by FDA, including Sleeping Buddha, plantain, and ephedra, among others. In the case of St. John's wort, published reports in 1999 suggested a potential for drug interactions[2] and a subsequent study by Piscatelli et al.[3] provided the needed scientific documentation to support a labeling change, which CHPA members adopted shortly after Piscatelli's study was published. CHPA shortly thereafter petitioned the agency to adopt the CHPA voluntary labeling program on St. John's wort into regulation.

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[2] Lantz, M.S. et al.: St. John's wort and antidepressant drug interactions in the elderly. *J. Geriatr. Psychiatry Neurol* 12(1):7-10, 1999. Johne, A. et al.: Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum). *Lancet* 355(9203):547-8, 2000.

[3] Piscitelli, S. C. et al.: Indinavir concentrations and St John's wort. *Lancet* 355(9203):547-8,2000.

Where the OTC and dietary supplement system differ, however, is in the nature and extent of support within their respective Centers. The Center for Drug Evaluation and Research (CDER) has a separate office for post-marketing surveillance and reasonably-well worked out operational procedures for evaluating and taking action on potential signals generated by the AER system, whether pertaining to drugs covered under New Drug Applications (NDAs) for which AER reporting is mandatory or to drugs marketed pursuant to the OTC Review, for which AER reporting is not mandatory.

CFSAN, on the other hand, does not give the same amount of resource support for AER management as CDER. There is no separate office within CFSAN for this purpose. CFSAN is unable to respond to FOI requests relating to its AER system in a timely fashion and does not keep its web-based component of its current system up-to-date. For the past two years, CFSAN has asked Congress for $2.5 million to develop its AER system, thereby demonstrating its current critical lack of resources.

With this perspective, the recommendations of the Inspection Report appear to be over-reaching, even to the point of adding complex systems over and above anything that CFSAN could handle.

2. **It is not the failing in the current AER system for dietary supplements that has led to the relatively low number of FDA actions, but rather: (a.) the generally excellent safety profiles of many dietary supplements; (b.) FDA's only recent commitment to engage a regulatory strategy for dietary supplements; and (b.) the current lack of a clear regulatory policy to initiate labeling changes once an AER signal has been scientifically documented.**

Further to the concern expressed in the Inspection Report's about the limited number of actions taken by the agency on dietary supplements (see page 3 of report), which is used as a reason why the system should be totally changed, the Inspection Report has overlooked several clear underlying reasons for the agency's relatively low number of actions, including the following:

a. The generally good safety profile of dietary supplements has contributed significantly to the low number of actions.

In Section 2 of the Dietary Supplement Health and Education Act of 1994 (DSHEA), Congress "identified 15 findings that were meant to establish a conceptual framework for Federal regulatory policy regarding dietary supplements."[4] Among these findings, Congress determined that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare." Certainly, the experience since the passage of DSHEA in 1994 upholds this finding. While there have been a handful of safety issues which FDA has addressed or is in the process of addressing (e.g., the contaminant, aristolochia; characterization of the new drug GBL

[4] Commission on Dietary Supplement Labels -- Final Report: Chapter I - Dietary Supplement Health And Education Act of 1994. Final Report Transmitted November 24, 1997.

as a dietary supplement; Sleeping Buddha; among several others), the mainstay dietary supplement ingredients (i.e., those with the greatest exposure to the American public, such as echinacea, ginseng, garlic, ginkgo, chondroitin, glucosamine, fiber, water soluble vitamins, fat soluble vitamins, and minerals, among many others) have demonstrated consistently highly acceptable safety profiles.

b. Furthermore, one of the most important factors in contributing to the conclusion of the Inspection Report that "FDA rarely takes safety actions" over the period of January 1994 to June 2000 is the fact that it was not until March 1999 that the FDA Commissioner (i.e., Dr. Jane Henney[5]) acknowledged that FDA has the tools it needs to regulate dietary supplements.

Hence, the period from October 1994 (passage of DSHEA) to March 1999 was a time of little commitment within FDA to support implementation of DSHEA. Following ex-Commissioner Henney's positive acknowledgement of FDA's authority under DSHEA in March 1999, the agency spent the remainder of 1999 convening Stakeholder sessions to develop its long-range plan for dietary supplements, which was issued in January 2000. Although the level of commitment to building the regulatory framework for dietary supplements clearly changed during the period of March 1999 to June 2000 (and beyond), CFSAN was still disadvantaged by personnel turn-overs and limited resources and funding, thereby being effectively unable to use the tools it had then, and still has, to follow post-marketing safety of dietary supplements.

Therefore, we do not agree with the Inspection Report conclusions that significant gaps in the structural framework of the current AER system led to the limited actions by FDA. Rather, we conclude that there was a critical dysfunction of the agency in the 4.5 years post DSHEA followed by a very recent rallying of the agency's efforts and resources by Dr. Jane Henny and Mr. Joe Levitt, and that the needed framework is in place, only needing adequate resources.

c. It is important to recognize that the current CFSAN administration has not set forth a policy to under-gird regulatory actions leading to mandatory labeling changes once the AER system has signaled a potential safety issue and subsequent scientific documentation has been developed to confirm the potential signal. As a result, FDA's inaction, even when it has evidence from the current AER system and support from industry, has been a result of the agency having no "end game" regulatory strategy/policy to bring closure to the findings within the AER system.

In this regard, it is important to note that for OTC monograph drugs there is a similar MedWatch-based AER system as for dietary supplements. This OTC monograph drug component of the system has also been sensitive to signals of potential safety

[5] Food and Drug Administration Commissioner Jane E. Henney, M.D. before the House Committee on Government Reform: "FDA has tools at its disposal to take enforcement actions against dietary supplements found to have safety, labeling, or other violations of the FD&C Act, as amended by DSHEA." March 25, 1999.

problems, as in the reported cases of allergic reactions to neosporin, which led to a CHPA petition requesting a label warning for neosporin-containing OTC drug products, or the reported cases of choking associated with taking water soluble gums when taken with insufficient water, which also led to a CHPA-initiated label warning requirement.[6] The significant difference between the OTC ingredient examples just named, however, and the example given above relating to St. John's wort is that FDA initiated reasonably rapidly a regulatory proceeding to act upon the scientific findings related to the OTC drug ingredients. To date, we have only been informed by FDA that the agency has not yet come to a conclusion about CHPA's Citizen Petitions relating to labeling of St. John's wort, labeling and packaging of ephedra, and labeling relating to use by pregnant and nursing women.[7]

It appears that CFSAN acknowledges this lack of scientific regulatory policy, since it lists as a "B" 2001 priority the development of guidance on "material fact" which relates to Section 201n of the Food, Drug Cosmetic Act, "failure to reveal a material fact."[8] This should clearly be a 2001 "A" priority, rather than a "B" priority, so as to facilitate actions on our Citizen Petitions (which were developed as requested regulatory outcomes to signals in the current AER system) as well as on future findings from future signals generated by the current AER system. Indeed, the Inspection Report's failure to address this significant issue speaks to its inherent limitations as a supporting document for initiating a total revamp of the current AER system.

In summary, these three key factors need to be considered in the Inspection Report in explaining the relative low number of FDA actions on dietary supplements, so a limited perspective or bias is not presented in the Report. The generally excellent safety profiles of many dietary supplements, FDA's only recently engaged commitment to a regulatory strategy for dietary supplements, and the current absence of a regulatory policy to initiate labeling changes once an AER signal has been scientifically documented, coupled with the fact that the current system works when operationally engaged, suggests the need to refine, not totally redefine or create, the current AER system for dietary supplements.

3. The Inspection Report omits a key assessment of the effectiveness of CFSAN's AER system – a review of CFSAN's internal operating procedures.

The Inspection Report purposefully "did not evaluate the internal operating procedures of the system" (see page 1, last sentence). This is a critical omission.

The stated purpose of the report was "to assess the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements in

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[6] See CHPA Citizen Petitions on water-soluble gum to Docket No.90N-0200 dated December 31, 1990, and January 4, 1991; CHPA Citizen Petition on topical antibiotics to Docket No. 95N-0062 dated June 20, 1992.

[7] See letter from FDA to CHPA dated December 15, 2000 re Docket No. 00p-1355/CP1.

[8] See FY 2001 CFSAN Program Priorities: "Develop guidance or regulation on safety information/material fact labeling for dietary supplements.

protecting the American consumer" (see "Purpose" on page 7). An assessment of the "effectiveness ... of the system" is integral to evaluating its current internal operating procedures, since such an evaluation would determine whether the gaps or shortcomings of the system were a function of processes, resources, level of staffing, inadequate internal guidance, etc. – all of which in and of themselves in a system able to generate signals (see above) could be entirely adequate explanations of the Inspection Report's conclusion that the current system is an "inadequate safety valve."

To underscore this, on April 27, 1999 CHPA made a Freedom of Information (FOI) request to the agency, asking for copies of all internal procedures, manuals, policies pertaining to CFSAN's current AER system for dietary supplements, including those relating to AE case management and personnel training (copy attached). To date, we have received no detailed reply to our FOI request. In a personal follow-up with a key policy manager within CFSAN, CHPA was told that CFSAN had no such written operating procedures or training manuals.[9] This exchange led to formal recommendations from CHPA to CFSAN to build the internal operating procedures for the current system.[10] We have received no response from CFSAN on our recommendations. See the Endnote for specific CHPA recommendations on building CFSAN's internal operating procedures for its AER system.

Had the OIG investigated the internal operating procedures of CFSAN's current AER system, we believe the Inspection Report would have focused on practical improvements to the current system, as opposed to over-reaching with recommendations for mandatory AER reporting and registration, which are not required for foods (and dietary supplements are foods). Furthermore, we also believe that the Inspection Report would have identified the need for a policy framework for initiating labeling on dietary supplement products (see above), including also a warning policy, which we have proposed to the agency.[11]

In sum, because OIG did not undertake an assessment of the operating procedures affiliated with CFSAN's AER system, we do not think the Inspection Report's conclusions are substantiated by the scope, nature, and level of "evidence" presented in the report. Without such a review, we do not see how the Inspection Report can come to meaningful conclusions and reasonable recommendations on "how well the system detects adverse event reports, generates signals of public health concerns, [and]

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[9] Personal communication from CFSAN's scientific staff member to CHPA scientific staff member.
[10] See Endnote and footnote #1.
[11] On several occasions, CHPA has commented to FDA's Center for Food Safety and Applied Nutrition that the Center needs to articulate a clear labeling policy on when to warn. FDA has a long standing policy that has been used for consumer products, including OTC medicines and foods, which is that warnings (or decisions about product availability) should be "scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer." The importance of such a policy openly acknowledged by the Center cannot be underestimated, as it focuses public health decisions on the first hurdle, scientific documentation, as the basis for decision making. See also: 47 *Federal Register* 1982: 54754; 53 *Federal Register* 1988: 46213; and Soller, R.W.: When to Warn. *Regulatory Affairs Focus* 2 (10): October 1997.

how well FDA addresses these signals and when necessary takes appropriate actions to protect consumers."[12]

4. A public awareness campaign is a reasonably, and entirely suitable, means to address certain limitations inherent in AER surveillance systems. Placing toll free numbers on all dietary supplements labels is not.

Limitations relating to the AER system for dietary supplements are not unique to this system. In fact, even in AER systems for drug products, such as OTC monograph ingredients, there are the same limitations relating to medical, product, manufacturer, and consumer use identified in the Inspection Report. However, the lack of outreach by CFSAN, as noted in the Inspection Report, may be a significant contributor to the "statistics" quoted on pages 18-21. With a concerted effort to inform consumers and physicians about the scope, nature and extent of information needed for meaningful reports to the MedWatch system, there would undoubtedly be significant improvement in the quantity and quality of the reports. Certainly, this approach should be undertaken first, in conjunction with improved resources, before other more stringent resource-intensive approaches are proposed.

While CHPA supports efforts to enhance awareness of the AER system for dietary supplements among health professionals and consumers, we do not think that the recommendation that the FDA's telephone number be placed on the package of all dietary supplements is appropriate suggestion to addressing the current shortcomings of the system, which as noted above stem principally from a weak policy structure and resource limitations. Aside from the fact that mandatory labeling of toll free numbers is not required for drugs or other foods, it is also troubling to consider how FDA would manage the shear volume of calls relating to non-serious and serious AERs as well as general consumer inquiries. Companies use toll free numbers on their labeling as much for consumer outreach and product development as for the management of validated serious AERs to their products. Only a subset of information relates to serious AERs, which is that cadre of AERs about which FDA and industry would be most interested from a safety standpoint. Expecting a consumer to evaluate seriousness vs. non-seriousness prior to using a toll free number on a label is simply unrealistic. Further, one toll free number on all products would likely detract from the use of local poison control numbers. The handling accidental overdose-related 24-hour emergency calls would also over-burden an FDA-managed AER system, and create a redundancy to the current national poison control system. Hence, mandatory labeling with a toll free number, while perhaps on the surface an attractive option, is on further in-depth reflection open to serious limitations and objections.

5. "Relatedness" of AERs should only be evaluated and used in the context of a dialogue among qualified experts, as a means to generate hypotheses about ingredient safety or in recommending formal public health actions.

[12] See page 8 of Inspection Report for quoted phrase.

The assertion in the Inspection Report that public disclosure of "relatedness" of the AER profile would be a useful form of risk management is a serious shortcoming (i.e., see pages 21 and 30), as noted in the following points:

- The consumer is unprepared to make a scientific judgement about anecdotal reports.
- AERs are by definition anecdotal and except in certain very highly selected circumstances for the most part useful only for hypothesis generating, requiring follow-up clinical or epidemiologic studies, as indicated elsewhere in the Inspection Report.
- Given the commentary in the Inspection Report that much information is missing from the AER, there is the very real likelihood that "relatedness" conclusions would be errors in judgement – either falsely implicating a product with a particular safety endpoint or, by contrast, falsely implying that the product is not related to the safety endpoint.
- Invariably "relatedness" judgements are inherently subjective, irrespective of how structured the process attempts to be; hence it is open to reviewer bias.

Thus, "relatedness" conclusions about AERs should be used only in scientific discussions about the safety of the ingredient/product (i.e., whether a drug, dietary supplement, conventional food, or cosmetic) or device by experts qualified in epidemiology, post-marketing surveillance and epidemiology. They should not appear on FDA's website, which is tardy in its updates and where incomplete information can be the difference between "possibly related" (which would be interpreted by the uniformed consumer as "related") and "not related."

In sum, the Inspection Report fails to recognize that possible or probable "relatedness" is interpreted as definite "causality" by the consumer. Posting "relatedness" ratings without due process of scientific investigation to adequately document scientifically the purported relationship between a dietary supplement and a reported adverse event amounts to regulation by fiat. This is not how the science of self care consumer products, whether dietary supplements or OTC drugs, should progress.

Summary Recommendations

In summary, a more reasonable approach to addressing the effectiveness of the current AER system for dietary supplements would be to refine the current capacities of the existing system, which would keep the level of regulatory requirements consistent with those required for conventional foods. Indeed, because of the lack of demonstrated commitment to implementing DSEHA until relatively recently, the apparent lack of defined operating procedures and policies for the current AER system, and the known ability of the current system to signal potential safety problems, we are led to the following three recommendations:

1. CFSAN should develop, if it has not already done so recently, detailed operating procedures for the current AER systems. As stated, for the first 4.5 years after the passage of DSHEA there were apparently no such procedures, highlighting the importance of assessing FDA's operating procedures as a basis for evaluating the effectiveness of the current system.

2. CFSAN should be given the funds and resources to: (a.) create and operate a state-of-the-art computer system for tracking and compiling AERs reportedly associated with dietary supplement use; (b.) manage FOI requests on AERs on a timely manner and keep the AER website updated. "Relatedness" conclusions should not appear on the website for the reasons given above; (c.) develop as a 2001 "A list" priority a regulatory policy framework for requiring label statements on dietary supplements, based on scientific documentation of signals in the AER system.

3. Importantly, mandatory AE reporting, registrations, and labeling requirements for toll free numbers is unnecessary as a means to have an effective safety valve in the form of an operationally-intact AER system within CFSAN.

In closing, feel free to contact me, should you wish clarification or follow-up to our remarks. Given that you provided us with a very short turn-around for reading the draft report, developing comments and obtaining member comments, we continue to review the report and may have additional comments in the future.

Sincerely yours,

R. William Soller, Ph.D.

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

cc: J. Levitt
C. Lewis, Ph.D.,

ENDNOTE

Excerpted from Page 4 of CHPA's Comments to Docket No. 99N-1174 pertaining to CFSAN's June 8, 1999 Stakeholder Meeting:

"Therefore, as stated in its May 27, 1999 comments to the House Committee on Government Reform, CHPA recommends:

a. "CFSAN prepare a written plan for and adopt a systems approach, similar to that recommended in FDA's May 1999 document "Managing the Risks from Medical Product Use: Creating a Risk Management Framework" to the management of

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Formerly Nonprescription Drug Manufacturers Association

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