

**DOCKET NO. 2007D-0388**

**BEFORE**  
**THE UNITED STATES OF AMERICA**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**

**COMMENTS OF THE**  
**AMERICAN HERBAL PRODUCTS ASSOCIATION**

**ON THE**  
**FOOD AND DRUG ADMINISTRATION'S**  
**DRAFT GUIDANCE TITLED**

**"QUESTIONS AND ANSWERS REGARDING ADVERSE EVENT REPORTING AND  
RECORDKEEPING FOR DIETARY SUPPLEMENTS AS REQUIRED BY THE  
DIETARY SUPPLEMENT AND NONPRESCRIPTION DRUG CONSUMER  
PROTECTION ACT"**

**December 14, 2007**

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA is comprised of domestic and foreign 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, including conventional human foods and dietary supplements.

## **Background**

The Dietary Supplement and Nonprescription Drug Consumer Protection Act was signed into law on December 22, 2006 and goes into effect on December 22, 2007. Although this law is self-implementing, it specifically requires the publication of guidance on “the minimum data elements that should be included in a serious adverse event report described under the amendments made by this Act.”

In a Federal Register notice published on October 15, 2007 (the October 15 notice), the Food and Drug Administration (FDA) announced the availability of a draft guidance titled, “Guidance for Industry: Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act” (the draft guidance). Both the October 15 notice and the draft guidance state that this guidance “is intended to assist the dietary supplement industry in complying with the serious adverse event reporting and recordkeeping requirements prescribed for dietary supplement manufacturers, packers, and distributors by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.” The draft guidance also states that it is intended to “describe the minimum data elements for serious adverse event reports for dietary supplements,” and that it provides guidance “on (1) how, when, and where to submit a serious adverse event report for a dietary supplement; and (2) records maintenance and access for serious and non-serious adverse event reports and related documents.”

AHPA and its members have an interest in the implementation of this new law. AHPA appreciates FDA’s publication of the draft guidance and the opportunity to provide comments to the draft guidance. AHPA has reviewed the draft guidance and offers the following comments.

### **FDA’s description of “inpatient hospitalization” is less clear than the instructions for MedWatch Form 3500A**

Question number 6 in the draft guidance is “What is a serious adverse event?” In response to this question, the draft guidance provides essentially the exact statutory language by which this term is defined. This definition includes “inpatient

hospitalization.” In a note within the response to this Question 6 and following this definition, the draft guidance adds:

FDA considers inpatient hospitalization to include initial admission to the hospital on an inpatient basis, even if the patient is released the same day, and prolongation of an existing hospitalization.

Based on ongoing reviews of adverse event reports submitted to FDA that are associated with dietary supplements, AHPA has observed that such reports are often generated by medical personnel who treat patients who seek medical advice at hospital emergency rooms but who are not admitted to the hospital. Absent any additional instruction at Question 6, AHPA is concerned that the act of seeking treatment at a hospital emergency room for a minor adverse event could be erroneously considered to be a serious adverse event.

AHPA notes that the instructions to the mandatory MedWatch Form 3500A provides the following information in discussing how that form should report hospitalization:

Hospitalization (initial or prolonged): Check if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

DO NOT check if:

- A patient in the hospital received a medical product and subsequently developed an otherwise nonserious adverse event, UNLESS the adverse event prolonged the hospital stay

DO check if:

- A patient is admitted to the hospital for one or more days, even if released on the same day
- An emergency room visit results in admission to the hospital

Note: Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious (medically important event).

AHPA believes that this last “note” provides important information, relevant to hospital emergency room visits that do not result in admission, that is not included in Question 6. AHPA therefore requests, to minimize erroneous classification of treatment at a hospital emergency room without actual admission as a serious adverse event, that FDA revise the draft guidance to add the same clarifying note that is provided in the instructions to MedWatch Form 3500A.<sup>1</sup>

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<sup>1</sup> AHPA notes that this same issue is addressed again in response to Question 13. AHPA further notes that although the same statement regarding FDA’s view of inpatient hospitalization is included there, there is also a footnote (footnote 2) which instructs the reader to “see Question 6.” AHPA suggests that if clarification is made

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**AHPA supports FDA's suggestion that all serious adverse events, regardless of route of receipt, be submitted within 15 days of receipt**

The draft guidance at Question 10 observes that the law specifies that serious adverse events that are received through the address or phone number on the label of a dietary supplement, as well as all follow-up reports of new medical information received by the responsible person within one year after the initial report, must be submitted to FDA no later than 15 business days after the report is received by the responsible person. FDA's response to this question goes on to observe that no such time requirement is specified for reports that are received by any other means (such as by email or by fax), and to recommend that all other such serious adverse event reports also be submitted within 15 days. AHPA agrees with this recommendation.

**AHPA agrees with FDA's identification of "Day 0"**

FDA's response in the draft guidance at Question 10 also notes that "Day 0 in the 15-business-day timeclock" established by the law is "the date the responsible person receives the minimum data elements," as defined elsewhere in the draft guidance. The agency expands on this guidance by adding, "If the responsible person does not initially receive sufficient data for a serious adverse event report to FDA, but later receives additional information completing the minimum data elements..., then the responsible person should submit the serious adverse event report within 15 business days of the date the additional information was received." AHPA agrees with both of these responses to Question 10.

**AHPA does not agree that responsible persons have any obligation to forward erroneously submitted reports**

In the final paragraph of FDA's response in the draft guidance to Question 10, the agency states:

Reports of serious adverse events received by a responsible person in which the initial reporter identifies the suspect dietary supplement as one manufactured, packaged, or distributed by another responsible person should be promptly forwarded to that other responsible person.

While AHPA can understand why FDA might take such a position as a suggestion, AHPA is concerned that to place this sentence in an official guidance document, without any clarification that such suggestion has no statutory basis, may have the effect of misrepresenting the legal obligations of a responsible person who receives a

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*(footnote continued from previous page)*

here at Question 6, footnote 2 can remain unchanged but the redundant description of FDA's view could be removed at Question 13.

report that has nothing to do with their dietary supplement product. AHPA therefore suggests that this recommendation be reworded, for example by repeating some of the language that was used in recommending that serious adverse event reports received through an email or a fax be submitted with 15 business days, as:

Although the FD&C Act does not expressly require a responsible person to take any action in the event that they receive reports of serious adverse events in which the initial reporter identifies the suspect dietary supplement as one manufactured, packaged, or distributed by another responsible person, the agency recommends that such reports be promptly forwarded to that other responsible person.

**AHPA agrees with FDA’s description of the “minimum data elements” and with the accompanying instruction to submit only complete reports**

FDA addresses the key issue of minimum data elements that must be included in any submitted serious adverse event report in Question 13 of the draft guidance and identifies five such minimum data elements: (1) an identifiable injured person (see AHPA’s next comment below to express concern about this specific language); (2) an identifiable initial reporter; (3) identity and contact information for the responsible person; (4) a suspect dietary supplement; and (5) a serious adverse event or fatal outcome. AHPA agrees that a report of a serious adverse event could not be complete without the inclusion of each of these elements.

AHPA notes that the agency in response to this question also states that the responsible person should “wait to submit a serious adverse event report to FDA until the [minimum data] information is obtained.” Further down in the response to this question, FDA provides a more explicit such instruction, stating, “if the initial reporter refuses to give the responsible person at least one way of contacting him or her for follow-up, such as a phone number or e-mail address, the responsible person should not submit a serious adverse event report to FDA because one of the minimum data elements for a report is missing.”

AHPA agrees that these are rational instructions but is concerned that companies that follow these instructions could be in violation of the statute. The statute does not provide any option for a responsible person to refrain from submitting a serious adverse event report just because one or another of the minimum data elements have not been made available by the reporter. AHPA therefore requests that FDA modify this response to clearly state that responsible persons who follow this guidance will not find themselves facing any kind of legal complaint by doing so.

**It is inconsistent with existing terminology to refer to the subject of an adverse event as “injured”**

As noted above, the first of the minimum data elements identified under Question 13 is “an identifiable injured person.” AHPA notes that the term “injured person” is not used

in other documents related to adverse event reports associated with other classes of goods under FDA's jurisdiction. For example, on MedWatch Form 3500A itself, as well as on the instructions to that form, the person who is the subject of an adverse event report, whether associated with a drug or medical device, is identified as a "patient." Similarly, in 21 CFR 301.305, the regulation related to prescription drug adverse event reports and records, such persons are referred to as the "patient" or "patients," or in one instance as the "subject." Even the guidance for industry that addresses the implementation of the Dietary Supplement and Nonprescription Drug Consumer Protection for nonprescription drugs (the nonprescription drug draft guidance)<sup>2</sup> that was published by FDA on the same date as the draft guidance refers to persons that are the subject of adverse events associated with nonprescription products as "patients," and not as "injured persons," such that one of the minimum data elements for submission to FDA of a serious adverse event for a nonprescription drug is "an identifiable patient."

AHPA has shown here that the use of the term "injured person" is inconsistent with existing terminology, and that a person who is the subject of an adverse event associated with a prescription or nonprescription drug or medical device is usually described in regulatory documents as a "patient" or "subject." AHPA believes that the implication of these terms is significantly different, and that there is a much more negative connotation associated with the term "injured person" than with the word "patient" or the word "subject." For these reasons, AHPA requests that the term "injured person" be replaced with the word "patient" or the word "subject" throughout the draft guidance, and further requests that the two paragraphs in the draft guidance under the heading "Identifiable injured person" in Question 13 be replaced in their entirety with the two paragraphs in the nonprescription drug draft guidance on page 4 under the heading "Identifiable patient."

**AHPA does not believe that the guidance should "encourage" use of health care practitioners to elicit information from reporters, except as an option**

One sentence in response to Question 13 states that the agency "encourages responsible persons to use trained health care practitioners to elicit information from reporters," and states that this is "to [the] end" of making "diligent attempts to obtain complete information." AHPA is strongly opposed to this recommendation, unless it is rephrased to be stated as an option to other means of obtaining complete information.

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<sup>2</sup> FDA, Center for Drug Evaluation and Research. October 2007. Guidance for Industry - Postmarketing adverse event reporting for nonprescription human drug products marketed without an approved application.

AHPA notes that this response goes on to suggest additional methods developed to obtain detailed information on an event, and specifically identifies “computer-assisted interview-technology,” and “targeted questionnaires.”

AHPA has expended considerable effort to create a targeted questionnaire to assist responsible persons to obtain detailed information on reported events. This questionnaire was developed with input from trained health care practitioners and was specifically designed to make sure that responsible persons will be well prepared to take thorough reports that provide not only the minimum data elements, but also all of the other information identified on MedWatch Form 3500A as well as additional relevant information. AHPA believes that properly trained staff using well-designed computer-assisted interview technology or targeted questionnaires can serve as an option to, rather than an adjunct to, the use of trained health care practitioners to make sure that complete information is obtained from reporters of adverse events.

AHPA therefore requests that the second and third sentences of the third paragraph in the response to Question 13 be combined to read as follows:

To this end, the agency encourages responsible persons to either use trained health care practitioners, or computer-assisted interview technology, targeted questionnaires, and/or other methods developed to obtain detailed information on an event to elicit information from reporters and to help focus the line of questioning.

**AHPA strongly disagrees that FDA’s “manufacturer B” need not submit a serious adverse event to FDA**

FDA describes a scenario in its response to Question 13 of a serious adverse event that “involves multiple suspect dietary supplements that were manufactured, packaged, or distributed by more than one responsible person (e.g., manufacturers A and B).” The agency goes on to suggest that only the first of these to receive a serious adverse event report (i.e., manufacturer A) should submit the report to FDA; that this first-contacted person should also communicate with the other person (i.e., manufacturer B); and that this second-contacted person (i.e., manufacturer B) “need not submit a separate report to FDA for the serious adverse event unless manufacturer B has information about the serious adverse event that was not provided to FDA in manufacturer A’s report.” AHPA believes this to be a seriously flawed approach.

Section 761(c)(3) of the Federal Food, Drug and Cosmetic Act (FFDCA), as revised by the Dietary Supplement and Nonprescription Drug Consumer Protection Act, states, “The Secretary shall develop systems to ensure that duplicate reports of, and new medical information related to, a serious adverse event shall be consolidated into a single report.” AHPA does not believe, however, that the best way to accomplish this

obligation is to instruct, through non-binding guidance, some responsible persons who receive a serious adverse event report to refrain from submitting the report to FDA because another responsible person already did so. AHPA believes that this suggested mechanism is likely to result in instances in which each of the responsible persons identified in a serious adverse event report that involves more than one dietary supplement will insist that they are “manufacturer B,” and therefore have no submission responsibility. Even in the event that manufacturer A does make the report, the law makes no provision to exempt other manufacturers from submitting duplicate reports; therefore manufacturer B would place itself in legal jeopardy by failing to submit the a report, even if a duplicate. AHPA strongly discourages any such suggestion in a final guidance on this matter.

### **FDA should provide guidance to submit “additional information”**

Question 15b asks whether “anything other than the product label” should be submitted with a serious adverse event report, and replies that the agency encourages the attachment, as appropriate, of “(1) hospital discharge summaries, (2) autopsy reports, (3) relevant laboratory data, and (4) other critical clinical data.”

AHPA notes that FFDCa section 761(d) states that serious adverse event reports submitted to FDA “may be accompanied by additional information,” and that section 761(f)(1) states that any such report “may be accompanied by a statement, which shall be a part of any report that is released for public disclosure, that denies that the report or the records constitute an admission that the product involved caused or contributed to the adverse event.”

AHPA believes that, for the draft guidance to fully and accurately represent whether “anything other than the product label” should be submitted with a serious adverse event report, the guidance must reference the law’s specific identification of this “additional information” and optional “statement,” and AHPA is requesting by this comment that Question 15b be revised to include these responses. AHPA is aware that the second of these two points is addressed in response to Question 27, but believes that it bears repeating in Question 15, as the wording of this question may lead responsible persons to believe that it provides an exhaustive list of “anything other than the product label” that should accompany a serious adverse event report.

### **FDA’s estimated annual recordkeeping burden is poorly substantiated**

In its discussion of recordkeeping in the October 15 notice, FDA offers the following information:

According to a 2001 report by the Office of the Inspector General, between 1994–1999 FDA received 2,547 adverse event reports involving dietary supplements, or about 500 reports per year, on average (Ref. 2). According to the report, the actual

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number of adverse events relating to dietary supplements is likely to be at least 100 times that many, or more than 50,000 adverse events per year.

The agency identifies "Ref. 2" as "Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve," Office of the Inspector General (OIG), Department of Health and Human Services, April 2001, OEI-01-00-00180. In addition, the agency states, "we are using the 50,000 per year figure as an upper bound estimate of reporting," such that the agency is apparently assuming that 100 percent of the adverse events that occur every year will be reported to a responsible person. The October 15 notice "requests comments on this estimate."

AHPA notes that the cited OIG report is not the initial source of the "100 times as many" estimate, and that this OIG report identifies its reference as A. Walker, "The Relation between Voluntary Notification and Material Risk in Dietary Supplement Safety," *FDA Commissioned Paper*, March 9, 2000. It should be recognized that this paper has never been published and there is nothing to indicate that it was peer-reviewed. AHPA is concerned about FDA's reliance on this single unreviewed document as the sole source of its "upper bound estimate" of the number of "adverse events [that] will be reported each year to the responsible person."

To begin with, the Walker paper's conclusion that a "best estimate is that less than one percent of serious adverse events caused by dietary supplements is reported to the FDA" is entirely speculative, and was made with absolutely no evaluation of the reporting rates of adverse events actually associated with dietary supplements. Instead, Walker considered what is known about systems that are in place in the United States and elsewhere to capture reports of adverse events associated with prescription drugs and vaccines, and then extrapolated a conclusion for dietary supplements.

An additional argument against reliance on this document to estimate the total number of reports that "will be reported each year to the responsible person" is that the document does not purport to measure that factor. Walker was concerned with estimating the percent of actual adverse events that are reported to FDA – not that are reported to manufacturers, packers, or distributors. Yet FDA has performed a calculation which results in a speculative total number of adverse event experiences. Without further comment, the agency then goes on with a presentation that apparently assumes that 100 percent of these events will be reported to the responsible person. This is almost certainly not a rational assumption, and it is most certainly not an assumption that is supported by the Walker paper.

In addition, AHPA wishes to place on the record the fact that this same FDA commissioned paper concludes that "the rate of reporting of drug and vaccine adverse events, even in countries where there are well-advertised and effective systems for

identifying events, is very low. It is probably no more than one percent, except when the event is readily recognized, severe, and clearly related to the exposure in the mind of the treating physicians” (emphasis added). AHPA believes that this information is material to any reference to this paper, and that it should be disclosed with any such reference.

### **Conclusion**

AHPA has provided these comments to express the views of the organization and its members on the issues raised by the draft guidance. AHPA requests that FDA take these comments into consideration before publishing a final guidance on this important subject.

AHPA appreciates the opportunity to provide these comments, and AHPA staff and counsel will make themselves available at any mutually convenient time to discuss any of the topics addressed herein.

Respectfully submitted,



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