DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2007D–0388]

Draft Guidance for Industry: Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and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; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled ''Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.'' This draft guidance is intended to assist the dietary supplement industry in complying with the serious adverse events reporting and recordkeeping requirements prescribed for dietary supplement manufacturers, packers, and distributors by the Dietary Supplement and Nonprescription Drug Consumer Protection Act. Separate guidance, issued by the Center for Drug Evaluation and Research on reporting for nonprescription (over-the-counter (OTC)) human drugs marketed without an approved application, is announced elsewhere in this issue of the **Federal Register**.

DATES: Submit written or electronic comments on the draft guidance document, including comments regarding proposed collection of information, by December 14, 2007.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Office of Nutritional Products, Labeling, and Dietary Supplements (HFS–800), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740. Send one self-addressed adhesive label to assist the office in processing your request, or include a fax number to which the draft guidance may be sent. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance.

Submit written comments on the draft guidance, including comments regarding proposed collection of information, to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to either *http://www.fda.gov/dockets/ecomments* or *http://www.regulations.gov*.

FOR FURTHER INFORMATION CONTACT: Vasilios Frankos, Center for Food Safety and Applied Nutrition (HFS–810), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–2375.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance entitled ''Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.'' On December 22, 2006, the President signed into law the Dietary Supplement and Nonprescription Drug Consumer Protection Act (the DSNDCPA) (Public Law 109–462, 120 Stat. 3469). This law amends the Federal Food, Drug, and Cosmetic Act (the act) with respect to serious adverse event reporting for dietary supplements and non-prescription drugs marketed without an approved application. The draft guidance document contains questions and answers relating to the new requirements under the DSNDCPA, concerning the mandatory reporting to FDA of serious adverse events associated with dietary supplements, the minimum data elements to be submitted in such reports, and records of serious and non-serious adverse events reported to a dietary supplement manufacturer, packer, or distributor.

The draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent FDA's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. ''Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth below.

With respect to the following collection of information, FDA invites comment on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.

Description of Respondents: Respondents to this collection of information are manufacturers, packers, and distributors of dietary supplements marketed in the United States.

The draft guidance presents FDA's recommendations for complying with the dietary supplement adverse event reporting and recordkeeping requirements of the act, as amended by the DSNDCPA. These requirements become effective on December 22, 2007.

A. Reporting

Under section 761(b)(1) of the act (21 U.S.C. 379aa–1(b)(1)), the manufacturer, packer, or distributor whose name (under section 403(e)(1) of the act (21 U.S.C. 343(e)(1))) appears on the label of a dietary supplement marketed in the United States is required to submit to FDA any serious adverse event report it receives regarding use of the dietary supplement in the United States, accompanied by a copy of the product label. In addition, under section 761(c)(2) of the act, the submitter of the serious adverse event report (referred to in the statute as the ''responsible person'') is required to submit to FDA a followup report of any related new medical information the responsible person receives within 1 year of the initial report.

The draft guidance discusses how, when, and where to submit serious

adverse event reports for dietary supplements and followup reports of new medical information. In accordance with the statutory requirements that serious adverse event reports for dietary supplements be submitted via MedWatch (section 761(d) of the act) and that FDA consolidate all information related to a serious adverse event into a single report (section 761(c)(3) of the act), the draft guidance directs the responsible person to submit serious adverse event reports on MedWatch Form 3500A and to attach a copy of the initial serious adverse event report on Form 3500A as part of any followup report of new medical information.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

	No. of respondents	Annual frequency per response	Total annual responses	Hours per response	Total hours
Serious adverse event reports for dietary supplements (21 U.S.C. 379aa–1(b)(1))	80	12	960	2	1,920
Followup reports of new medical information (21 U.S.C. 379aa–1(c)(2))	20	12	240	1	420
Total					2,160

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

B. Reporting Burden

Because mandatory reporting of serious adverse events for dietary supplements does not become effective until December 22, 2007, FDA has no data on mandatory dietary supplement adverse event reports from past years to use in developing a burden estimate. However, FDA currently collects voluntarily-submitted adverse event reports for dietary supplements. Industry, health care providers, and consumers voluntarily submit several thousand reports annually to FDA's Center for Food Safety and Applied Nutrition (CFSAN) through the CFSAN Adverse Events Reporting System (CAERS), which contains reports of adverse events associated with conventional foods, dietary supplements, and cosmetics. According to a Congressional Budget Office Cost Estimate (Ref. 1), in 2005 CAERS received almost 500 reports of adverse events suspected to be related to dietary supplements.

Only manufacturers, packers, and distributors of dietary supplements are required to report adverse events for these products to FDA, and only if the firm's name appears on the label of the dietary supplement associated with the adverse event. Moreover, reporting is required only for those adverse events defined as ''serious.'' FDA does not know how many of the 500 reports of dietary supplement adverse events voluntarily submitted in 2005 would have been considered serious, nor how many of these reports originated from or were reported to the manufacturer, packer, or distributor whose name appears on the label of the dietary supplement associated with the adverse event. As a rough estimate for planning purposes, CAERS staff estimate that they will receive about 80 serious adverse event reports relating to dietary supplements each month. Thus, we estimate that the number of dietary supplement serious adverse event reports submitted to FDA annually will total 960 reports (12 x 80 reports per month). FDA requests comments on this estimate.

FDA's Center for Drug Evaluation and Research estimates it will take respondents a total of 2 hours to collect information about a serious adverse event associated with an over-the-counter drug marketed without an approved application and report the information to FDA on MedWatch Form 3500A. That time burden estimate is based on FDA's knowledge of the adverse drug experience reports submitted to the agency for nonprescription drug products marketed under an approved application, including knowledge about the time needed to prepare the reports. FDA believes that the time for a dietary supplement firm to collect information about a serious adverse event associated with a dietary supplement and report the information to FDA will be approximately the same, as MedWatch Form 3500A will be used in both cases; therefore, we also estimate this time burden at 2 hours per report. The estimated total annual burden for dietary supplement serious adverse event reports is shown in row 1 of table 1 of this document.

If a firm that has submitted a serious adverse event report receives new medical information related to the serious adverse event within 1 year of submitting the initial report, the firm must provide the new medical information to FDA in a followup report. Given our lack of experience with mandatory dietary supplement adverse event reporting, we do not have any information on the number of followup reports of new medical information that will be submitted to FDA each year. We expect followup medical information to be reported for some percentage of the 960 serious adverse event reports we estimate receiving annually. In the absence of data that would support a more precise estimate, we will assume that 25 percent of the 960 serious adverse event reports for dietary supplements will have a followup report submitted. FDA requests comments on this estimate. We estimate that each followup report will require an hour to assemble and submit, including the time needed to copy and attach the initial serious adverse event report as recommended in the draft guidance. We assume the followup report will take less time than the initial serious adverse event report, as the responsible person will not need to fill out Form 3500A for the followup report. FDA requests comments on whether the burden estimate of 1 hour is reasonable for this information collection. The estimated total annual burden for followup reports of new medical information is shown in row 2 of table 1 of this document.

C. Recordkeeping

Section 761(e)(1) of the act requires that responsible persons maintain records related to dietary supplement adverse event reports they receive, whether or not the adverse event is serious. Under the statute, the records must be retained for a period of 6 years. The draft guidance provides FDA's recommendations as to what records

industry should maintain to satisfy the statutory recordkeeping requirement.

The guidance recommends that the responsible person document its attempts to obtain the minimum data elements for a serious adverse event report. Along with these records, the guidance recommends that the responsible person keep the following other records: (1) Communications between the responsible person and the initial reporter of the adverse event and with any other person(s) who provided information about the adverse event; (2) (for serious adverse events only) the responsible person's serious adverse event report to FDA on MedWatch Form 3500A, with attachments; (3) any new medical information about the adverse event received by the responsible person; (4) (for serious adverse events only) any reports to FDA of new medical information related to the serious adverse event report. We estimate that assembling and filing these records, including any necessary photocopying, will take approximately 0.5 hours per adverse event report received by the responsible person.

Once the documents pertaining to an adverse event report have been assembled and filed, FDA expects the records retention burden to be minimal, as the agency believes most establishments would normally keep this kind of record for at least several years after receiving the report, as a matter of usual and customary business practice. FDA requests comment on current adverse event recordkeeping practices in the dietary supplement industry, including the length of time such records are typically kept.

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 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. In the absence of data on how many adverse events will be reported each year to the responsible person once the DSNDCPA becomes effective in December 1997, we are using the 50,000 per year figure as an upper bound estimate of reporting. This is almost certainly an overestimate of the number of reports the firms will receive, as it is unlikely that every adverse event that occurs will be reported to the responsible person. FDA requests comments on this estimate.

We estimated in the economic impact analysis of the Dietary Supplement Good Manufacturing Practices final rule (the GMP final rule) (72 FR 34752, June 25, 2007) that there are 1,460 manufacturers, packers, and holders of dietary supplements (72 FR 34752 at 34920). We assume that the estimated 50,000 adverse event reports related to dietary supplements will be spread evenly among these firms. The estimate of the number of manufacturers, packers, and holders of dietary supplements from the GMP final rule is FDA's best estimate of the number of firms that are ''responsible persons'' who must comply with the recordkeeping requirements of the DSNDCPA; however, it is not a precise estimate because the number of dietary supplement establishments covered by the GMP final rule is likely to be larger than the number of ''responsible persons,'' where a ''responsible person'' is a dietary supplement manufacturer, packer, or distributor whose name is listed on the label of a dietary supplement marketed in the United States (see section 761(b)(1) of the act). Thus, FDA's estimate for the number of respondents in table 2 may be overinclusive. FDA requests comments on the number of firms that would be subject to the recordkeeping requirements of the DSNDCPA.

The estimated total annual recordkeeping burden under the statute and this guidance is shown in table 2 of this document.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

	No. of recordkeepers	Annual frequency per recordkeeping	Total annual records [2]	Hours per record	Total hours
Dietary supplement adverse event records (21 U.S.C. 379aa–1(e)(1))	1,460	4.2465	50,000	0.5	25,000
Total					25,000

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] For purposes of estimating the number of records and hours per record, a ''record'' means all records kept for an individual adverse event report received by the responsible person.

III. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding the draft guidance, including comments regarding proposed collection of information. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IV. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. S. 3546 Dietary Supplement and Nonprescription Drug and Consumer Protection Act, Congressional Budget Office Cost Estimate, December 27, 2006.

2. ''Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve,'' Office of the Inspector General, Department of Health and Human Services, April 2001, OEI–01–00–00180.

V. Electronic Access

Persons with access to the Internet may obtain the draft guidance at *http://www.cfsan.fda.gov/guidance.html*.

Dated: October 10, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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