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

0910-0635

SUPPORTING STATEMENT

Terms of Clearance: OMB approved this collection under the condition that it be reported as a violation since this information was previously collected without OMB approval. In 2009, FDA reported this collection as a violation in the ICB.

A. Justification

1. Circumstances Making the Collection of Information Necessary

The Dietary Supplement and Nonprescription Drug Consumer Protection Act (the DSNDCPA) (Public Law 109–462, 120 Stat. 3469) amends the Federal Food, Drug, and Cosmetic Act (the FD&C Act) with respect to serious adverse event reporting and recordkeeping for dietary supplements and non-prescription drugs marketed without an approved application. Section 761(b)(1) of the FD&C Act (21 U.S.C. 379aa-1(b)(1)) requires the manufacturer, packer, or distributor whose name (pursuant to section 403(e)(1) of the FD&C Act (21 U.S.C. 343(e)(1))) appears on the label of a dietary supplement marketed in the United States to submit to FDA all serious adverse event reports associated with the use of a dietary supplement, accompanied by a copy of the product label. The manufacturer, packer, or distributor of a dietary supplement is required by the DSNDCPA to use the MedWatch form (FDA 3500A) when submitting a serious adverse event report to FDA. In addition, under section 761(c)(2) of the FD&C 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 follow-up report of any related new medical information the responsible person receives within 1 year of the initial report.

As required by section 3(d)(3) of the DSNDCPA, FDA issued guidance to describe the minimum data elements for serious adverse event reports for dietary supplements. In the Federal Register of July 14, 2009 (74 FR 34024), FDA announced the availability of guidance entitled "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 guidance discusses how, when, and where to submit serious adverse event reports for dietary supplements and follow-up reports. The guidance also provides FDA's recommendation on records maintenance and access for serious and non-serious adverse event reports and related documents.

FDA is requesting OMB approval of the information collection provisions in the guidance and the following statutory citations:

21 U.S.C. 379aa-1(b)(1) – Reporting

Serious adverse event reports for dietary supplements – Section 761(b)(1) of the FD&C Act (21 U.S.C. 379aa-1(b)(1)) requires the manufacturer, packer, or distributor whose name (under section 403(e)(1) of the FD&C Act (21 U.S.C. 343(e)(1)) appears on the label of a dietary supplement marketed in the United States submit to FDA any serious adverse event report it receives regarding use of dietary supplements in the United States.

21 U.S.C. 379aa-1(c)(2) – Reporting

Follow-up reports of new medical information – Section 761(c)(2) of the FD&C Act (21 U.S.C. 379aa-1(c)(2)) requires the responsible party to submit to FDA a follow-up report of any new medical information received within one year of the initial report.

21 U.S.C. 379aa-1(e)(1) -- Recordkeeping

Maintenance of records of dietary supplement adverse events – Section 761(e)(1) of the FD&C Act (21 U.S.C. 379aa-1(e)(1)) requires that responsible persons maintain for six years records related to dietary supplement adverse event reports they receive, whether or not the adverse event is serious.

2. Purpose and Use of the Information Collection

The FDA will receive the information as required by the DSNDCPA with respect to serious adverse event reporting for dietary supplements. The reporting and recordkeeping requirements for serious adverse events related to dietary supplements are important for public health reasons. Reporting of serious adverse events to FDA will serve as an early warning sign of potential public health issues associated with dietary supplements. Without notification of all serious adverse events associated with dietary supplements, FDA would be unable to investigate and follow up promptly, which in turn could cause delays in alerting the public when safety problems are found. In addition, the information received will provide a reliable mechanism to track patterns of adulteration in food that would support efforts by FDA to target limited inspection resources to protect the public health.

Description of Respondents: The likely respondents include businesses engaged in the manufacture, packing, or distribution of dietary supplements marketed in the United States. Respondents are from the private sector (for-profit businesses).

3. Use of Improved Information Technology and Burden Reduction

Mandatory dietary supplement adverse event reports currently are submitted to FDA on the MedWatch form, Form FDA 3500A. FDA is not able to receive these reports electronically at this time. However, FDA is developing a method by which mandatory dietary supplement adverse event reports may be electronically submitted to the agency via the FDA Safety Reporting Portal (the SRP). The SRP, originally part of the

MedWatch[Plus] system, was approved by OMB under control number 0910-0645. FDA is developing a new rational questionnaire for the submission of mandatory dietary supplement adverse event reports via the SRP. FDA will submit the new rational questionnaire for OMB review under control number 0910-0645. The agency expects to implement the new rational questionnaire in FY 2014. Thus, FDA will submit the revised ICR for 0910-0645 to OMB in FY 2013. Once the new rational questionnaire is implemented, the agency estimates that about seventy-five percent (75%) of the mandatory dietary supplement adverse event reports will be submitted electronically.

4. Efforts to Identify Duplication and Use of Similar Information

There is no duplication of reporting requirements as a result of the mandatory reporting requirement in the DSNDCPA. The manufacturer, packer, or distributor of a dietary supplement is required by statute to use a MedWatch form when submitting a serious adverse event report to FDA. The statute permits but does not require FDA to modify the MedWatch form for dietary supplement serious adverse event reporting. The agency has determined that MedWatch Form 3500A, the form used for mandatory reporting of adverse events for other FDA-regulated products, is also the most appropriate MedWatch form currently available for mandatory reporting of dietary supplement serious adverse events.

5. Impact on Small Businesses or Other Small Entities

FDA estimates that eighty percent (80%) of respondents are small businesses. The reporting and recordkeeping requirements are mandated by the DSNDCPA and there is no statutory exception for small businesses. The reporting and recordkeeping provisions discussed in the guidance are also applicable to all businesses including small businesses. However, FDA aids small businesses in complying with its requirements through the agency's Regional Small Business Representatives and through the scientific and administrative staffs within the agency. FDA has provided a Small Business Guide on the agency's website at http://www.fda.gov/oc/industry/.

6. Consequences of Collecting the Information Less Frequently

Data collection occurs occasionally. The DSNDCPA requires that serious adverse event reports received through the address or phone number on the label of a dietary supplement, as well as follow-up reports of new medical information received by the responsible person within one year after the initial report, be submitted to FDA no later than 15 business days after the report is received by the responsible person. FDA believes that prompt, mandatory reporting is consistent with the Congressional intent of the DSNDCPA and important for public health reasons. Delayed or less frequent reporting of some serious adverse events to FDA would lessen the effectiveness of adverse event reporting as an early warning sign of possible safety problems with dietary supplements. Without notification of all serious adverse events associated with dietary supplements, FDA would be unable to investigate and follow-up promptly, which in turn could cause delays in alerting the public when safety problems are found.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

As discussed above, this collection of information involves more than quarterly submission of information to the agency and written responses to the agency in less than 30 days. The DSNDCPA requires that serious adverse event reports, as well as follow-up reports of new medical information received by the responsible person within one year after the initial report, be submitted to FDA no later than 15 business days after the report is received by the responsible person. This may result in submission of information to FDA on a basis that is more frequent than quarterly. As discussed above, this collection of information involves retention of records for more than three years. Section 761(e)(1) of the FD&C Act requires that responsible persons maintain for six years records related to dietary supplement adverse event reports they receive, whether or not the adverse event is serious. This collection of information does not involve submission of more than an original and 2 copies, the use of statistical methods, pledges of confidentiality by FDA not supported by authority established in statute or regulation, or require the disclosure of trade secrets or other confidential information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), in the Federal Register of March 23, 2012 (77 FR 17076), FDA published a 60-day notice requesting public comment on the proposed extension of this collection of information ("the March 23 Notice"). FDA received one timely letter in response to the notice, containing multiple comments.

(Comment 1) One comment suggested that FDA underestimated the burden hours associated with reporting serious adverse events. The comment proposed that FDA's estimate of 2 hours per report is too low and stated that the estimate should be in the range of 2 to 10 hours per report. The comment also suggested that FDA did not fully consider the time needed to acquire the required information. The comment stated that time is needed to determine whether the event is serious or non-serious and third parties such as medical experts are frequently used to make a determination.

(Response) FDA disagrees. FDA appreciates the information provided in the comment that a range from 2 to 10 hours should be estimated per report, but no data was offered to support this position. Based upon the information found in CFSAN's Adverse Events Reporting System database, two hours is an accurate approximation of the amount of time required to file a report. The agency also notes that its estimate of two hours per report does fall within the range suggested by the comment. Accordingly, FDA believes the estimate of 2 hours per report for serious adverse events is appropriate.

(Comment 2) One comment suggested that FDA did not account for the time to maintain non-serious adverse event reports. Also, the comment stated that non-serious adverse events are more frequently reported and accounts for the majority of the time spent as part of the mandatory recordkeeping requirement.

(Response) FDA disagrees. Table 2 presents FDA's calculations for the time to maintain all adverse event reports pursuant to 21 U.S.C. 379aa-1(e)(1). FDA estimates there are approximately 1,600 dietary supplement manufacturers, packers, or distributors that are subject to adverse event mandatory recordkeeping, thus FDA estimates that there are a total of 1,600 recordkeepers. FDA further estimates that each recordkeeper will keep approximately 74 records per year, for a total of 118,400 records. The agency estimates that assembling and filing these records, including any necessary photocopying, will take approximately 30 minutes, or 0.5 hours, per record. Therefore, 118,400 records x 0.50 hours = 59,200 total hours. FDA bases its estimates on its experience with similar adverse event reporting programs.

(Comment 3) One comment stated that FDA incorrectly estimated that there is no capital costs associated with reporting and recording serious adverse events. The comment suggested that FDA did not fully consider that firms invest significant capital resources in systems for capturing post-market surveillance data, software, staff training, re-training, and third-party experts.

(Response) FDA disagrees. The Agency believes the comment mischaracterizes the costs associated with hiring third-party experts, obtaining systems for capturing post-market surveillance data and software, and training and re-training of staff as capital costs. For purposes of information collection requests under the Paperwork Reduction Act, capital costs are costs for equipment, machinery, and construction that, if not for FDA's request or requirement, the respondent would not incur. This includes buying specialized software and computer equipment; monitoring, sampling, drilling and testing equipment; record storage facilities; the cost of purchasing or contracting out information collection services; and, postage costs to mail in a report. Capital costs do not include costs to achieve regulatory compliance with requirements of the FD&C Act not associated with the information collection. Under section 402(f) of the FD&C Act, a dietary supplement is adulterated if it presents a significant or unreasonable risk of illness or injury. Section 402(g) of the FD&C Act provides that a dietary supplement is adulterated if it has been prepared, packed, or held under conditions that did not meet current good manufacturing practices. Further, section 403(a) of the FD&C Act proscribes a dietary supplement from being misbranded. In general, manufacturers and distributors of dietary supplements are responsible for ensuring that their products are safe and compliant with all applicable statutes and regulations, so actions like hiring third parties to determine serious and non-serious adverse events, paying for a surveillance system and software to capture data for post-market surveillance, and training staff to use such a system are costs associated with complying with the FD&C Act (sections 402(f) and (g) and 403(a)) and other obligations. Thus, these costs are not a capital cost because they are costs associated with achieving regulatory compliance with requirements of the FD&C Act, not costs associated specifically with filing a report pursuant to 761(b)(1) or (c)(2) of the FD&C Act or maintaining records pursuant to 761(e)(1) of the FD&C Act.

9. Explanation of Any Payment or Gift to Respondents

FDA does not provide any payments or gifts to respondents.

10. Assurance of Confidentiality Provided to Respondents

Section 761(f)(2) of the FD&C Act (21 U.S.C. 379aa-1(f)(2)) provides that a serious adverse event report submitted to FDA, including any new medical information submitted, shall be considered a record about an individual under section 552a of title 5, United States Code (commonly referred to as the "Privacy Act of 1974") and a medical or similar file the disclosure of which would constitute a violation of section 552 of such title 5 (commonly referred to as the "Freedom of Information Act"), and shall not be publicly disclosed unless all personally identifiable information is redacted.

11. Justification for Sensitive Questions

This information collection does not contain questions that are of a personally sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

Description of Respondents: The likely respondents include businesses engaged in the manufacture, packing, or distribution of dietary supplements marketed in the United States. Respondents are from the private sector (for-profit businesses).

12a. Annualized Hour Burden Estimate

FDA estimates the burden for this information collection as follows:

Hour Burden Estimate

TABLE 1.--ESTIMATED ONE-TIME AND RECURRING REPORTING BURDEN[1]

21 U.S.C. Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
21 U.S.C. 379aa-1(b)(1)- serious adverse event reports for dietary supplements	480	17	8,160	2	16,320
21 U.S.C. 379aa-1(c)(2) – follow-up reports of new medical information	120	17	2,040	1	2,040
Total recurring burden					18,360

[1]There are no capital costs or operating costs associated with the collection of information under this statutory requirement.

Reporting

This estimate is based on FDA's experience with similar adverse event reporting programs and the number of serious adverse event reports and follow-up reports received in the past 2 years. All dietary supplement manufacturers, packers, or distributors are subject to serious adverse event mandatory reporting. FDA estimates that, in 2012, there are approximately 1,600 such firms, based on the estimate of 1,460 provided in the Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements final rule (72 FR 34751, June 25, 2007), with a two to three percent annual rate of growth applied.

FDA received 830 initial serious adverse event reports in FY2010. The number of reports more than doubled to 1,777 in FY2011. We expect this trend to continue and, in fact, increase due to continued industry compliance with mandatory reporting rules. Based on this, FDA expects to receive over the next three years an increasing number of reports per year: we estimate that we will receive 3,500 in 2012; 7,000 in 2013; and 14,000 in 2014; for an annual average of 8,166.66 per year, rounded to 8,160. Based on the agency's records, the average number of initial reports per year on a per firm basis during 2010 and 2011 was 17. Thus, FDA estimates that, on average over the next three years, 480 firms will file 17 initial dietary supplement serious adverse event reports, for a total of 8,160 total annual responses.

FDA estimates that it will take respondents an average of 2 hours per report to collect information about a serious adverse event associated with a dietary supplement and report the information to FDA on Form FDA 3500A. Thus, the estimated total annual hour

burden of initial dietary supplement serious adverse event reports is 16,320 hours (8,160 responses x 2 hours) as shown in row 1 of Table 1.

If a respondent that has submitted a serious adverse event report receives new information related to the serious adverse event within one year of submitting the initial report, the respondent must provide the new information to FDA in a follow-up report. FDA estimates that 25 percent of serious adverse event reports related to dietary supplements will have a follow-up report submitted, resulting in approximately 2,040 follow-up reports submitted annually (8,160 x 0.25 = 2,040). Assuming that 25 percent of submitters of initial reports will submit follow-up reports (480 x 0.25 = 120) and the average number of follow-up reports per year per firm to be 17, FDA estimates that, on average over the next three years, 120 firms will file 17 follow-up reports, for a total of 2,040 total annual responses. We estimate that each follow-up 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 guidance. The estimated total annual hour burden for follow-up reports of new information is 2,040 hours (2,040 responses x 1 hour) as shown in row 2 of Table 1.

The total reporting hour burden is 18,360 hours, which equals the burden for the mandatory reports (16,320) plus the burden for the follow-up new information (2,040).

TABLE 2.-- Estimated Annual Recordkeeping Burden[1]

21 U.S.C. Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
21 U.S.C. 379aa-1(e)(1)- dietary supplement adverse events records	1,600	74	118,400	0.5 (30 minutes)	59,200
Total recordkeeping burden					59,200

[1]There are no capital costs or operating costs associated with the collection of information under this interim final rule.

Recordkeeping

All 1,600 dietary supplement manufacturers, packers, or distributors, are subject to serious adverse event mandatory recordkeeping, thus FDA estimates that there are a total of 1,600 recordkeepers. FDA further estimates that each recordkeeper will keep approximately 74 records per year, for a total of 118,400 records. The agency estimates that assembling and filing these records, including any necessary photocopying, will take approximately 30 minutes, or 0.5 hours, per record. Therefore, 118,400 records x 0.50 hours = 59,200 total hours. FDA bases its estimates on its experience with similar adverse event reporting programs.

Once the documents pertaining to an adverse event report have been assembled and filed pursuant to the Safety Reporting Portal, 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.

12b. Annualized Cost Burden Estimate

Reporting Cost Burden Estimate

The total annual hour cost burden to respondents is approximately $1,851,055.20 per year. FDA estimates that the average hourly wage for an employee to prepare and submit an adverse event report and follow-up medical information would be equivalent to a GS-14/Step-1 level in the locality pay area of Washington-Baltimore in 2012, which is $50.41/hour. Doubling this wage to account for overhead costs, FDA estimates the average hourly cost to respondents to be $100.82/hour. Thus, the overall estimated cost incurred by the respondents is $1,851,055.20 (18,360 burden hours x $100.82/hour = $1,851,055.20).

Recordkeeping Cost Burden Estimate

FDA estimates the recordkeeping hour burden costs to be about $50.41 ($100.82 x 0.5 hours) per record kept. This estimate is based upon the records being kept by an employee making a salary equivalent to a GS-14/Step 1 level in the locality pay area of Washington-Baltimore in 2012, which is $50.41/hour. Doubling this wage to account for overhead costs, FDA estimates the average hourly cost to recordkeepers to be $100.82/hour. Thus, the total recordkeeping cost burden to be $5,968,544 (=$50.41 per record x 118,400 records).

13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

There are no capital costs or operating and maintenance costs associated with this collection.

14. Annualized Cost to the Federal Government

The initial evaluation of a dietary supplement adverse event would include reviewing the case, reviewing related literature, writing a summary of the case, and providing an opinion about the association between the product(s) and the adverse event(s) and documenting the clinical review into CAERS database. This task would take between 1-2 hours. A more in-depth analysis of an adverse event(s) such as looking for adverse event patterns, or signal detection of an adverse event(s) being associated with a product and then rewriting up summarized reports to supervisors, could take between 40 to 60 hours or much longer depending on the number of cases needed to be analyzed, complexity of the cases and related literature research.

Therefore, we estimate that on average it will take 1.5 hours for an initial evaluation. The cost of each evaluation would be about $196.59 (1.5 hours x $131.06 per hour). This estimate is based upon the evaluation being done by an employee making a salary equivalent to a GS-14-10 level in the locality pay area of Washington-Baltimore in 2012, which is $65.53/hour. Doubling this wage to account for overhead costs, FDA estimates the average hourly cost to the Federal Government to be $131.06/hour.

The in-depth analysis of each adverse event we estimate on average will take 50 hours. The cost of each in-depth analysis would be about $6,553 (50 hours x $131.06 per hour). This estimate is based upon the analysis being done by an employee making a salary equivalent to a GS-14-10 level in the locality pay area of Washington-Baltimore in 2012, which is $65.53/hour. Doubling this wage to account for overhead costs, FDA estimates the average hourly cost to the Federal Government to be $131.06/hour.

We estimate FDA will receive 8,160 serious adverse event reports annually making the total annual cost to the Federal Government for the initial evaluation and in-depth analysis of all reports $55,076,654.40 ($6,749 x 8,160).

15. Explanation for Program Changes or Adjustments

The burden estimate for the subject ICR was inadvertently underreported in ICRAS/ROCIS in 2009. This error has been corrected in this ICR; the previously underreported recordkeeping burden now appears as IC#3 in ICRAS/ROCIS.

This is an extension request in which both the total annual number of responses and the total annual hour burden are being increased. The total annual number of responses increased from 828 to 128,600 responses (an increase of 127,772 responses) and the total annual hour burden has increased from 1,490 to 77,560 hours (an increase of 76,070 hours). The increase was due to three factors: 1) the correction of an error in the previous ICRAS/ROCIS submission; 2) industry growth, resulting in an increased number of respondents and recordkeepers; and, 3) increased industry compliance with mandatory reporting rules. Thus, we are characterizing the increases as adjustments.

TABLE 3—Summary of Change in Responses and Hour Burden

IC Number	Change in Responses	Change in Hour Burden
IC#1	+7,498	+14,996
IC#2	+1,874	+1,874
IC#3	+118,400	+59,200
Total Change	+127,772	+76,070

For IC#1, we estimate that the respondents have increased from 55 to 480, causing the annual number of responses to increase from 662 to 8,160 (an increase of 7,498 responses) and the annual hour burden to increase from 1,324 to 16,320 (an increase of 14,996 hours). We are characterizing the increase as an adjustment because it is based on

the increase in the number of reports received by FDA in FY 2010 and FY 2011, caused by increased industry compliance with mandatory reporting rules and industry growth.

For IC#2, we estimate that the respondents have increased from 14 to 120, causing the annual number of responses to increase from 166 to 2,040 (an increase of 1,874 responses) and the annual hour burden to increase from 166 to 2,040 (an increase of 1,874 hours). We also are characterizing this increase as an adjustment because it is based on the increase in the number of reports received by FDA in FY 2010 and FY 2011.

For IC#3, we have made an adjustment by adding a new IC to correct an error (missing recordkeeping burden estimate) in the previous ICRAS/ROCIS submission. In 2007 and 2008, FDA published 60-day and 30-day Federal Register notices containing both a reporting burden table and a recordkeeping burden table. Unfortunately, the ICRAS/ROCIS submission in 2008 contained only two ICs, both of which concerned the reporting burden table. The recordkeeping annual hour burden inadvertently was not included. This also caused the annual number of records to be underreported. For 2012, we have created a new IC to correctly report the recordkeeping burden hours and records. The new IC increases recordkeepers from 0 to 1,600, causing the annual number of records to increase from 0 to 118,400 (an increase of 118,400 records) and the annual hour burden to increase from 0 to 59,200 (an increase of 59,200 hours).

16. Plans for Tabulation and Publication and Project Time Schedule

We are not publishing any information received as a result of this information collection.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

We are not seeking approval to not display the expiration date for OMB approval of the information collection.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.