

SUPPORTING STATEMENT FOR REPORTING & RECORDKEEPING  
REQUIREMENTS - ADVERSE DRUG EXPERIENCE REPORTING

0910-0230

Expires April 30, 2009

Docket Number 2005N-0157

A. JUSTIFICATION

1. **Circumstances of Information Collection**

Sections 201, 502, 505, and 701 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321, 352, 355, and 371) require that marketed drugs be safe and effective. In order to know whether drugs that are not safe and effective are on the market, FDA must be promptly informed of adverse experiences occasioned by the use of marketed drugs. In order to help ensure this, FDA issued regulations at §§ 310.305 and 314.80 (21 CFR 310.305 and 314.80) to impose reporting and recordkeeping requirements on the drug industry that would enable FDA to take action necessary for protection of the public health from adverse drug experiences.

All applicants who have received marketing approval of drug products are required to report to FDA serious, unexpected adverse drug experiences, as well as followup reports when needed (§314.80(c)(1)). This includes reports of all foreign or domestic adverse experiences as well as those obtained in scientific literature and from postmarketing epidemiological/surveillance studies. Under §314.80(c)(2), applicants must provide periodic reports of adverse drug experiences. A periodic report includes, for the reporting interval, reports of serious, expected adverse drug experiences and all non-serious adverse drug experiences, a narrative summary and analysis of adverse drug experiences and a history of actions taken because of adverse drug experiences. Under §314.80(i), applicants must keep for 10 years records of all adverse drug experience reports known to the applicant.

For marketed prescription drug products without approved new drug applications or abbreviated new drug applications, manufacturers, packers, and distributors are required to report to FDA serious, unexpected adverse drug experiences as well as followup reports when needed (§310.305(c)). Under §310.305(f) each manufacturer, packer, and distributor shall maintain for 10 years records of all adverse drug experiences required to be reported.

The primary purpose of FDA's adverse drug experience reporting system is to provide a signal for potentially serious safety problems with marketed drugs. Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the larger and more diverse patient populations exposed to the marketed drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects. Signals are obtained from a variety of sources, including reports from patients, treating physicians, foreign regulatory agencies, and clinical investigators. Information derived from the adverse drug experience reporting system contributes directly to increased public health protection because the information enables FDA to make important changes to the product's labeling (such as adding a new warning) and when necessary, to initiate removal of a drug from the market.

## **2. Purpose and Use of Information**

The regulations require the reporting to FDA of important adverse drug experience information associated with the use of unapproved-marketed prescription drug product. This information is used by FDA to determine at the earliest possible time whether to request a manufacturer, packer, or distributor to recall a product from the market or to recommend a seizure or injunction action to halt the marketing of the product and to remove it from the market. Such action, initiated promptly, may avert further adverse effects

that may be associated with the use of the product. The consequence of not conducting this collection of information is that FDA would be unable to monitor the safety of these marketed drug products so as to assure that these drug products are not adulterated or misbranded.

Concerning approved drug products, the primary purposes of FDA's adverse drug experience reporting system is to signal potentially serious safety problems, focusing especially on newly marketed drugs. Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the larger and more diverse patient population exposed to the marketed drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects. Signals are obtained from a variety of sources, including reports from patients, treating physicians, foreign regulatory agencies, and clinical investigators. Information derived from the adverse drug experience reporting system contributes directly to increased public health protection because such information enables FDA to make important changes to the product's labeling (such as adding a new warning) and, when necessary, to initiate removal of a new drug from the market.

### 3. Use of Improved Information Technology

The regulations give the respondents the option to submit reports of adverse drug experiences by computerized formats. FDA encourages the submission of all aspects of an NDA by computer, and has made available guidances describing the procedures to be followed (see paragraphs below). Much of the information required by 21 CFR 314.80 is to be submitted on Form FDA-3500A. To facilitate reporting, manufacturers may use a computer-generated format, provided that this other format is agreed to by FDA.

In the Federal Register of December 11, 2003, FDA issued a final rule amending FDA regulations governing the format in which

certain labeling is required to be submitted for review with NDAs, certain BLAs, ANDAs, supplements, and annual reports. The final rule requires the electronic submission of the content of labeling (i.e., the content of the package insert or professional labeling, including all text, tables, and figures) in NDAs, certain BLAs, ANDAs, supplements, and annual reports electronically in a form that FDA can process, review, and archive.

The following guidances for industry have been developed to improve the use of information technology in the submission of marketing applications for human drugs and related reports:

- "Providing Regulatory Submissions in Electronic Format--NDAs" (January 28, 1999). This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs.
- "Providing Regulatory Submissions in Electronic Format--General Considerations" (January 28, 1999). This guidance includes a description of the types of electronic file formats that the agency is able to accept to process, review, and archive electronic documents. The guidance also states that documents submitted in electronic format should enable the user to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page while maintaining fonts, special

orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents.

- "Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format" (November 12, 1999). This guidance provides information to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA).

- "Providing Regulatory Submissions in Electronic Format-- Prescription Drug Advertising and Promotional Labeling" (January 31, 2001). This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.

- "Providing Regulatory Submissions in Electronic Format--ANDAs" (June 27, 2002). This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.

- "Providing Regulatory Submissions in Electronic Format--Annual reports for NDAs and ANDAs" (August 2003). This guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.

- "Providing Regulatory Submissions in Electronic Format-- Postmarketing Periodic Adverse Drug Experience Reports" (June 2003). This guidance discusses general issues related the

electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

- "Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Product Applications and Related Submissions" (August, 2003). This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional material.
- "Providing Regulatory Submissions in Electronic Format--General Considerations" (October 2003). This draft guidance discusses general issues common to all types of electronic regulatory submissions.
- "Providing Regulatory Submissions in Electronic Format--Content of Labeling" (February 2004). This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

These guidance documents are available at FDA's web site <http://www.fda.gov/cder/guidance/index.htm>.

#### 4. **Efforts to Identify Duplication**

There are no other regulations requiring the reporting to FDA of adverse drug experience information on approved or unapproved-marketed prescription drug products. In order to avoid unnecessary duplicate reporting of the same incident and for the same product, the regulation permits packers and distributors, instead of

submitting adverse drug experience reports to FDA, to submit the reports to the manufacturer of the drug product who then must comply with all of the reporting requirements.

5. **Involvement of Small Entities**

The requirements of this regulation apply equally to all manufacturers, packers and distributors (large and small) of approved and unapproved marketed prescription drug products. FDA applies its regulations equally to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. A small business coordinator has been assigned to the Commissioner's staff to ensure that small businesses have an adequate opportunity to express their concerns and to keep FDA management apprised of how regulatory decisions might impact the small business community. To provide additional assistance to small businesses, FDA has established an office whose exclusive concerns are to provide small businesses with help in dealing with FDA regulatory requirements.

6. **Consequences if Information Collected Less Frequently**

The prescribed frequencies for reporting are based upon FDA's view that reporting to FDA important adverse drug experience information associated with the use of an unapproved marketed prescription drug product is sufficiently similar to that for an approved prescription drug product (i.e., protection of the public health) to warrant similar reporting requirements in most instances. Less frequent data collection would delay identification of drugs believed responsible for adverse reactions including fatalities and permanent injuries. Appropriate FDA action such as withdrawal of the drug from the market or changes in labeling would be delayed by less frequency.

7. **Consistency with the Guidelines in 5 CFR 1320.6**

Under § 310.305, the collection of information is inconsistent with 5 CFR 1320.6 in the following respects:

a. The regulation requires reporting of serious unexpected adverse drug experiences and follow up reports within less than 30 days. Reports to FDA are required within 15 working days of receipt of information. Reports to a manufacturer by a packer and distributor are required within 3 days of receipt of information. This shorter time period is necessary because these are the adverse drug experiences most likely to reveal serious safety problems with the drug and, thus, potentially can result in the need for agency action.

b. The regulation requires retention of records for a period of time longer than 3 years. The regulations require retention of records for a period of 10 years. The 10-year retention period is to assure that respondent records, which include raw data and any correspondence relating to an adverse drug experience, are available in evaluating long-term or other rare or latent effects like carcinogenicity that might be detected after several years of marketing experience.

Concerning § 314.80, the regulations require justification for requesting respondents to report more often than quarterly. The sponsor of an NDA is required to notify FDA of any unexpected adverse reactions within 15 working days of receipt of information on such a reaction by the sponsor. This shorter time for reporting is necessary so that FDA is informed as soon as possible of any serious problems with a drug product, and so that the agency can take appropriate action. The maintenance period for keeping these records is 10 years which is also inconsistent with 5 CFR 1320.6. This extended period is due to the potential litigation, matters of public safety due to drug interactions in addition to the adverse drug experiences and need for studies of delayed effects such as

carcinogenicity. This is actually a reduction in the retention period from the previous NDA regulatory requirement of indefinite retention.

8 **Consultation Outside the Agency**

In the Federal Register of May 3, 2005 (70 FR 22882), FDA published a notice requesting comments on the information collection burden. One comment was received on the burden estimates.

The comment said that it was not clear what methodology and assumptions were used by FDA to calculate either the annual reporting burden or the annual recordkeeping burden of the proposed collection of information.

FDA response: As stated in the May 3, 2005, Federal Register notice, the estimates are based on FDA's knowledge of adverse drug experience reporting, including the time needed to prepare the reports, and the number of reports submitted to FDA during 2004.

The comment said that §§ 310.305(c)(5) and 314.80(c)(1)(iii) in the first two rows of Table 1 refer to drugs without approved marketing applications and nonapplicants, respectively, rather than applicants. The comment contended that the citations used for these rows should be § 314.80(c)(1)(i) and (ii), which refer to the requirements for submission of initial and follow-up 15-day alert reports by the holders of approved marketing applications, or additional rows should be added to the table to include these additional reporting requirements. The comment also said that

FDA's estimates of the burden of adverse experience reporting for 15-day alerts, periodic reports, and recordkeeping seem grossly underestimated, and that the discrepancy cited above concerning § 314.80(c)(1)(i) and (ii) may account for the apparent underestimation of number of respondents and annual frequency of responses. The comment noted that it submitted 6,107 15-day alert reports to FDA in 2004, and that this alone exceeds the total burden reported in Table 1.

FDA response: FDA agrees that Table 1, as presented in the May 3, 2005, Federal Register notice is misleading. There is an inadvertent omission of the first sentence of the footnote that appears under Table 1. That footnote reads: "There are no capital costs or operating and maintenance costs associated with this collection of information." The footnote should read: "The reporting burden for §§ 310.305(c)(1), (c)(2), and (c)(3), and 314.80(c)(1)(i) and (c)(1)(ii) was reported under OMB control number 0910-0291. There are no capital costs or operating and maintenance costs associated with this collection of information." (This correct version of the footnote appeared in earlier Federal Register notices requesting OMB extension of this information collection. See, for example, the Federal Register of July 22, 2002 (67 FR 47821)). OMB control number 0910-0291 refers to the information collection package for FDA's MedWatch program and forms ("MedWatch: Food and Drug Administration Medical Products

Reporting Program"). The most recent request for OMB approval of this package was published in the Federal Register of August 16, 2005 (70 FR 48157), and OMB recently approved the package until October 31, 2008. MedWatch Form FDA 3500A is used to comply with the requirements in §§ 310.305(c)(1), (c)(2), and (c)(3), and 314.80(c)(1)(i) and (c)(1)(ii). The remaining requirements for adverse experience reporting for human drugs are covered in this package (0910-0230).

Concerning periodic reports, the comment said the annual frequency per response (an estimate the comment assumed to be the average number of periodic reports submitted per company) is estimated by FDA to be 20, and that this is considerably less than the 218 periodic reports that the comment said it submitted in 2004.

FDA response: The column in Table 1 titled "Total Annual Responses" refers to the number of periodic reports submitted annually per company. FDA estimates 10,614 reports annually.

The comment also said that the estimate of the hours required to prepare each periodic report is underestimated and only seems to reflect the time needed to compile the report and write the narrative sections. The estimate does not reflect the additional time required to collect, prepare, solicit and process follow-up information for each individual FDA Form 3500A report. The comment estimated that these activities take approximately 90

minutes for each FDA Form 3500A, and that a true estimate of the hours to prepare a periodic report should include at least an additional 1.5 hours for each non-15-day report that is contained within each periodic report.

FDA response: Based on the information provided by the comment to prepare and submit in the periodic report information pertaining to 15-day Alert reports and non-15-day Alert reports, FDA has revised the estimate for the time required to prepare and submit each response under § 314.80(c)(2) to approximately 60 hours per response.

The comment said that it does not understand how the annual frequency, total annual reports, and total hours are calculated for the estimated annual recordkeeping burden. The comment said that it needs to store each individual 15-day Alert report, each individual non-15-day FDA Form 3500A, and each individual periodic report. The comment said that FDA's estimates seem to indicate that each company has one document to store. The comment said that it annually submits more than 6,000 15-day Alert reports and 200 periodic reports containing many thousands of non-15-day FDA Form 3500As. Because of this, the comment said that it spends well over the one hour allotted by FDA to each company for these activities.

FDA response: FDA estimates that approximately 400,000 records are maintained by applicants under § 314.80(i). This

estimate is based on the information provided by the comment concerning 15-day Alert reports and non-15-day Alert reports, on the approximate number of 15-day Alert reports and non-15-day Alert reports received by FDA annually, and the fact that § 314.80(i) also requires that records of "raw data and any correspondence relating to adverse drug experiences" be maintained. FDA also estimates that approximately 16 hours are required to maintain each record (under § 314.80(i) as well as § 310.305(f)). Therefore, the total hours for records maintenance under § 314.80(i) is approximately 6,400,000.

The comment also disagreed with FDA's statement that there are no capital costs, operating, or maintenance costs associated with the collection of 15-day alert and periodic reports. The comment said that it (and other pharmaceutical companies) develop and maintain or purchase expensive, validated databases to collect and process adverse event information. These systems must continually be enhanced to accommodate new regulatory initiatives, such as the electronic submission of individual case safety reports in accordance with the ICH E2B guidelines. The comment said that companies must purchase servers (sometimes multiple servers worldwide), and each employee needs hardware and software. Support services for these systems are also quite expensive. The comment also said that companies must license MEDDRA each year to meet the international standards for common reporting terminology.

The comment said that costs for computer systems vary widely, but can amount to millions of dollars per year, especially for larger companies, and that capital and operational expenses for safety databases average \$7.6 million per year. The comment also questioned the statement that there are no capital, operating, or maintenance costs associated with maintaining records of adverse experience reports for ten years. The comment said that companies must maintain facilities to store what amounts to large volumes of paper records, in addition to back-up records on other media (scanned optical images, microfilm, and so forth). The comment said that costs for storage and retrieval vary widely, depending on the volume of records, rental fees, transportation costs, and retrieval fees, but can be substantial (e.g., thousands of dollars per year). The comment said that its storage and retrieval expenses are approximately \$22,000 per year.

FDA response: Based on the information provided by the comment, FDA estimates that the capital costs or operating and maintenance costs associated with records maintenance is approximately \$22,000 annually. Although the comment did not suggest a specific cost associated with the reporting requirements, FDA estimates that the capital costs or operating and maintenance costs associated with the reports submitted to FDA is approximately \_\_\_\_\_ annually.

The comment said that it is important for the FDA to move

quickly to change their periodic reporting requirements to be consistent with the ICH Guidelines for periodic safety update reports. The comment said that this will enable companies to submit the same report to all regulatory authorities globally, and will decrease the burden involved with preparing unique periodic reports specifically for FDA. Additionally, for those companies who have received a waiver from FDA to submit periodic reports in the periodic safety update report format, the comment said that this would decrease the burden of adding US-specific appendices to the reports. The comment also said that periodic safety update reports submitted to FDA should not routinely include any information in addition to that included in the ICH Guidelines for periodic safety update reports. The comment noted that FDA should not require full copies in either paper or electronic form of cases that were not subject to expedited reporting. If a potential signal arises about a specific product, FDA has the authority and opportunity to request all available information associated with any individual case(s). The comments said that greater collaboration between FDA and companies when FDA identifies a potential signal would facilitate better pharmacovigilance. For example, case reports should be shared and mutually discussed.

The comment also said that electronic submission of 15-day alert reports would decrease the reporting burden, and that FDA

requirements for electronic submission should be harmonized with EMEA requirements, so pharmaceutical companies do not have to develop and validate separate programs.

The comment also said that cost savings could be realized by both FDA and companies by eliminating the requirement for submitting original literature articles as attachments to 15-day alert reports. Articles would always be available to FDA on request. Alternatively, if there was electronic reporting, the literature article could be submitted electronically as an attachment in accordance with the ICH E2B guidance.

The comment also said that cost savings could also be realized by eliminating the requirement to collect non-serious labeled events. Costs associated with collecting information that has little, if any, value has a substantial financial impact on both companies and the agency.

The comment also said that it supports FDA's efforts to consider provisions for alternate methods of data storage other than through hard copy paper records. Companies prefer to choose and maintain methods for storage and retrieval of records according to the individual company's needs. Storing scanned optical images of records instead of paper copies would considerably decrease the need for large file rooms, extensive offsite storage facilities, and the costs associated with maintaining these facilities.

FDA response: FDA is in the process of revising its safety reporting and recordkeeping regulations. In the Federal Register of March 14, 2003 (68 FR 12406), FDA proposed to amend its pre- and postmarketing safety reporting regulations for human drug and biological products to implement definitions and reporting formats and standards recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's (WHO's) Council for International Organizations of Medical Sciences (CIOMS). The rulemaking is also intended to codify FDA's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed drugs and licensed biological products, to require that certain information be submitted to FDA in an expedited manner, to clarify certain requirements, and to make other minor revisions. FDA also proposed to amend its postmarketing annual reporting regulations for human drug and licensed biological products to revise the content for these reports. In the proposed rule, FDA said it is taking this action to strengthen its ability to monitor the safety of human drugs and biological products. The intended effect of the changes would be to further worldwide consistency in the collection of safety information and submission of safety reports, increase the quality of safety reports, expedite FDA's review of critical safety information, and enable FDA to protect and promote

public health. FDA said that the proposed changes would be an important step toward global harmonization of safety reporting requirements and additional efforts are underway within the Department of Health and Human Services to harmonize the reporting requirements of U.S. Federal agencies (e.g., FDA and the National Institutes of Health (NIH) are continuing to work together to address the best ways to streamline information sharing and harmonize, to the extent possible, the safety reporting requirements of the two agencies).

9. **Remuneration of Respondents**

FDA has not provided and has no intention to provide any payment or gift to respondents under this provision.

10. **Assurance of Confidentiality**

Release of information submitted to FDA in adverse drug experience reports is governed by 21 CFR Part 20. The regulation also urges manufacturers, packers, and distributors not to include names and addresses of individual patients in adverse drug experience reports; instead, some other identifier, such as initials or code numbers, should be included.

11. **Questions of a Sensitive Nature**

No questions of a private or sensitive nature are asked.

12. **Estimates of Annualized Hour Burden to Respondents**

Respondents to this collection of information are manufacturers, packers, distributors and applicants. FDA estimates the burden of this collection of information as follows:

Table 1. -- Estimated Annual Reporting Burden<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total annual Responses	Hours Per Response	Total Hours
310.305(c)(5)	1	1	1	1	1
314.80(c)(1)(iii)	5	1	5	1	5
314.80(c)(2)	530	20	10,614	60	636,840
Total					636,846

<sup>1</sup>The reporting burden for §§310.305(c)(1), (c)(2), and (c)(3), and 314.80(c)(1)(i) and (c)(1)(ii) was reported under OMB No. 0910-0291. The capital costs or operating and maintenance costs associated with this collection of information are \_\_\_\_\_ annually.

Table 2. -- Estimated Annual Recordkeeping Burden<sup>1</sup>

21 CFR Section	No of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
310.305(f)	25	1	25	16	400
314.80(i)	530	1	400,000	16	6,400,000
Total					6,400,400

<sup>1</sup> The capital costs or operating and maintenance costs associated with this collection of information are \$22,000 annually.

These estimates are based on FDA's knowledge of adverse drug experience reporting, including knowledge about the time needed to prepare the reports and the number of reports submitted to the agency.

### 13. Estimates of Annualized Cost Burden to Respondents

Based on an average hourly cost to industry of \$50 per hour (including overhead and benefits), the total annual cost burden to industry would be \$351,862,300 (7,037,246 x \$50).

### 14. Estimates of Annualized Cost Burden to the Government

Approximately 10,620 drug experience reports that are accounted for in this information collection assessment are reviewed annually by FDA personnel. Each report required about 30 minutes for review and follow-up. At an FDA labor cost of approximately \$50 per hour, the cost to the Federal Government is \$531,000 (10,620 x 50).

**15. Changes in Burden**

The changes in this burden are the result of an increase in the burden hours to comply with the requirements and in the number of periodic report submissions (see # 8 above). All of the adverse drug experience reporting and recordkeeping regulations are currently being revised (see the Federal Register of March 14, 2003 (68 FR 12406)). Once this rulemaking process is completed, these estimates will be revised accordingly and consolidated under one submission.

**16. Time Schedule, Publication and Analysis Plans**

There are no publications.

**17. Exemption for Display of Expiration Date**

The required reporting forms accurately reflect the OMB approval number.

**18. Certifications**

There are no exceptions to the certification statement identifier in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I