

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

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 (§§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. 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.

### 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. 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 a respondent records, which include raw data and any correspondence relating to an adverse drug experience, are available in evaluation 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 short time for reporting is necessary so that FDA is informed as soon as possible of any serious problems with a drug product, 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 old NDA regulatory requirement of indefinite retention.

## 8 **Consultation Outside the Agency**

In the Federal Register of February 25, 2002 (67 FR 8545), the agency requested comments on the proposed collection of information. FDA received 2 comments.

The comments asked what methodology and assumptions were used by FDA to calculate the burden estimates.

The "hours per response" were based on FDA's estimates of the time it would take manufacturers, packers, distributors, and applicants of marketed human drug products to submit the information to the agency.

The comments said that the annual number of responses of periodic reports is significantly underestimated. One comment estimated that companies submit more than 400 periodic reports (annual and quarterly reports) annually. The other comment estimated that it submits over 70 periodic reports annually.

FDA data indicates that it receives, on average, approximately 10,245 periodic reports (annual and quarterly reports) annually. A periodic report includes, as previously indicated, a narrative summary, individual case safety reports, and history of actions taken. Although some companies may submit 400 periodic reports annually, others only submit 1 periodic report annually.

The comments stated that the burden estimate seems to reflect only FDA's effort and not that of the respondents. The comments said that the hours per response for preparing periodic reports is grossly underestimated. One comment said that the preparation, quality control, and duplication of NDA periodic reports takes, on average, from 16 to 40 hours each, while the other comment said that this

processing takes from 100 to 300 hours for each periodic report. The comments said that all adverse experience reports, including the non-15-day alert reports, need to be taken into account when calculating the burden, because all need to be reviewed, assessed, and processed for determination of "expedited" status and for inclusion in the periodic safety update reports. For example, the comments said that one company received approximately 49,000 initial adverse drug experience reports in association with their marketed prescription products from worldwide sources in 2001, approximately 4800 of which qualified as 15-day alert reports; this included both initial and follow-up reports. Another company received approximately 20,000 initial adverse event reports from worldwide sources in 2001, approximately 2000 of which qualified as 15-day alert reports; this included both initial and follow-up reports.

FDA notes that the estimate of 5 hours in the February 25, 2002, notice was a typographical error. The correct estimate should be 28 hours. As explained in the information collection notice that published in the Federal Register of January 29, 1999 (64 FR 4665), this estimate is based on industry suggestions.

The comments questioned whether there are no capital, operating, or maintenance costs associated with maintaining records of adverse experience reports for 10 years. The comments said that companies must maintain facilities to store paper records in addition to back-up records on other media. Costs for storage and retrieval vary widely, depending on the volume of records, rental fees, transportation costs, and retrieval fees, but may be substantial (i.e., thousands of dollars annually).

FDA agrees that there are maintenance costs associated with maintaining records of adverse experience reports for 10 years. FDA estimates that these costs are approximately \$2000 per company annually, as suggested by the comments.

The comments also provided several suggestions on how the regulations should be revised to enhance the reporting efficiency and to minimize the burden of the collection of information. For example, the comments said that FDA should revise the requirements to be consistent with the International Conference on Harmonization (ICH) guidelines for periodic safety update reports.

FDA is in the process of revising its safety reporting and recordkeeping regulations and will consider these comments in finalizing its rulemaking. Respondents will have an opportunity to comment further on these rulemaking initiatives. As stated in the Federal Register of May 13, 2002 (67 FR 33059), FDA is planning to publish a proposed rule that would amend the expedited and periodic safety reporting regulations for human drugs and biologics to revise certain definitions and reporting formats as recommended by the ICH and to define new terms; to possibly add to or revise current reporting requirements; to consider revising certain reporting time frames; and to suggest other revisions to these regulations to enhance the quality of safety reports received by FDA.

The most recent consultations with the public has been FDA's participation in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and with the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS). These organizations have met periodically over the past five years to facilitate international consideration of issues, particularly safety issues, concerning the use of both foreign and domestic data in the development and use of drugs and biological products. The organizations include representative from government, associations, and the pharmaceutical industry (including PhRMA) from the European Union, Japan, and the U.S. ICH has produced several adverse drug reaction reporting guidances that pertain to expedited safety reporting, periodic safety reporting, and electronic submission of

reports. FDA is currently revising its regulations to be consistent with the ICH recommendations.

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	Number of Respondent	Annual Frequency per Respondent	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)	683	15	10,245	28	286,860
Total					286,866

<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.

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

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

21 CFR Section	No of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeping	Total Hours
310.305(f)	25	1	25	1	25
314.80(i)	683	1	683	1	683
Total					708

<sup>1</sup> There are no capital costs or operating costs associated with this collection of information. There are maintenance costs of \$35,400 (708 x \$50) 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, the total annual cost burden to industry would be \$14,378,700 (287,574 x \$50).

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

Approximately 10,251 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 \$42 per hour (based on the adjusted industry labor cost per hour), the cost to the Federal Government is \$430,542 (10,251 x 42).

**15. Changes in Burden**

The changes in this burden are the result of a decrease in the number of periodic report submissions. All of the adverse drug

experience reporting and recordkeeping regulations are currently being revised. 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

023002ss.doc 7/3/02