DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005N–0157]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Postmarketing Adverse Drug Experience Reporting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: OMB is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Management Programs (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1482.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Postmarketing Adverse Drug Experience Reporting—21 CFR 310.305 and 314.80 (OMB Control Number 0910–0230)—Extension

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 enabling FDA to take the action necessary to protect 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 nonserious 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.

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[1]

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	10,600	60	636,000

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]—Continued

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Total					636,006

[1]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. The capital costs or operating and maintenance costs associated with this collection of information are approximately $25,000 annually.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

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

[1]There are no capital costs or operating costs associated with this collection of information. There are maintenance costs of $22,000 annually.

These 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 the agency during 2004.

In the **Federal Register** of May 3, 2005 (70 FR 22882), FDA published a 60-day notice requesting public comment on the information collection provisions (the May 2005 notice). 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 responds that, as stated in the May 2005 notice, the estimates are based on FDA's knowledge of adverse dug 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 in the May 2005 notice 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 (c)(1)(ii), which refer to the requirements for submission

of initial and followup 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 (c)(1)(ii) may account for the apparent underestimation of the 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 of the May 2005 notice.

FDA responds that the agency agrees that Table 1, as presented in the May 2005 notice is misleading. There is an inadvertent omission of the first sentence of the footnote that appears under Table 1 of the May 2005 notice. 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 (OMB control number 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 responds that the column in Table 1 of the May 2005 notice, entitled ''Total Annual Responses'', refers to the number of periodic reports submitted annually per company. FDA estimates 10,614 reports annually.

The comment 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 followup 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 responds that 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 responds that the agency 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 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 International Conference on Harmonisation (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 the Medical Dictionary for Regulatory Activities 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 10 years. The comment said that companies must maintain facilities to store what amounts to large volumes of paper records, in addition to backup 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 responds that 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. The comment did not suggest a specific estimate for capital costs or operating and maintenance costs associated with reports submitted to FDA. FDA believes that many of the costs discussed by the comment that pertain to submitting reports

to FDA are standard operating procedures for most pharmaceutical companies. However, FDA is estimating a cost of approximately $25,000 annually for maintenance costs resulting from the reporting requirements. FDA specifically requests comment on this estimate.

The comment said that it is important for FDA to move quickly to change periodic reporting requirements to be consistent with 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 U.S.-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 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 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 European Agency for the Evaluation

of Medicinal Products requirements, so pharmaceutical companies do not have to develop and validate separate programs.

The comment 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 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 companies' 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 responds that the agency 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 and by the World Health

Organization's Council for International Organizations of Medical Sciences. 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 that 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 are continuing

to work together to address the best ways to streamline information sharing and to harmonize, to the extent possible, the safety reporting requirements of the two agencies).

Dated: January 30, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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