Supporting Statement A

REPORTING & RECORDKEEPING
REQUIREMENTS - ADVERSE DRUG EXPERIENCE REPORTING

A. JUSTIFICATION

1. **Circumstances Making the Collection of Information Necessary**

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 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 follow-up reports when needed (§ 314.80(c)(1)). This includes reports of all foreign or domestic adverse experiences as well as those based on information from applicable scientific literature and certain reports from postmarketing studies. Section 314.80(c)(1)(iii) pertains to such reports submitted by non-applicants. 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 and an index of these reports, 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)). Section 310.305(c)(5) pertains to the submission of followup reports to reports forwarded by FDA. 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 provide 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), decisions about risk evaluation and mitigation strategies or the need for postmarket studies or clinical trials, and when necessary, to initiate removal of a drug from the market.

2. Purpose and Use of the Information Collection

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 and Burden Reduction**

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. These guidance documents are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm. 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 and Use of Similar Information**

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. **Impact on Small Businesses or Other 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 of Collecting the Information 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. **Special Circumstances Relating to the Guidelines of 5 C.F.R. § 1320.5**

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 **Efforts to Consult Outside the Agency**

In the Federal Register of March 20, 2012 (77 FR 16232), FDA published a 60-day notice requesting comments on this information collection. One commenter raised the issue of the quality of the reports having an impact on the ability to identify product-specific issues. A recent analysis conducted by Tufts Center for the Study of Drug Development was cited indicating that certain key elements of adverse event reports are often missing or incorrect and that product names can be spelled in variable ways or misspelled. FDA agrees that data reported to FDA and entered into our product safety databases should be as accurate and complete as possible. FDA is considering these factors as we continue to develop the FDA Adverse Event Reporting System (FAERS) to replace the current AERS system. FDA received other comments, but they did not pertain to the information collection in 21 CFR 310.305(c)(5) and (f), and 314.80(c)(1)(iii), (c)(2), and (i).

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 Provided to Respondents**

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. **Justification for Sensitive Nature**

There are no questions of a sensitive nature.

12. **Estimates of Annualized Burden Hours and Costs**

12a. Annualized Hour Burden Estimate

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	No. of Responses per Respondent	Total annual Responses	Average Burden per Response	Total Hours
310.305(c)(5)	3	1	3	1	3
314.80(c)(1)(iii)	5	1	5	1	5
314.80(c)(2)	665	22.85	15,195	60	911,700
Total					911,708

[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 No. 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	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
310.305(f) 314.80(i)	25 665	1 601.50	25 399,998	16 16	400 6,399,968
Total					6,400,368

[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.

13. **Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs**

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 $388,868,300 (7,777,366 x $50).

14. Annualized Cost to the Federal Government

CDER devotes approximately 835 FTEs ($270K per FTE for 1 CDER reviewer for FY 2011) to the review of applications and other submissions under 21 CFR 314, including the periodic report submissions under § 314.80.

15. Explanation for Program Changes or Adjustments

The changes in this burden are the result of a revision in the number of periodic report submissions. 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)). In 2010, FDA published rulemaking that finalized part of the March 14, 2003, proposal (75 FR 59935, September 29, 2010). After FDA finalizes the remainder the proposal, these estimates will be revised accordingly and consolidated under one submission.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

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

The required reporting forms accurately reflect the OMB approval number.

18. Exception to Certification for Paperwork Reduction Act Submissions

There are no exceptions.