UNITED STATES FOOD & DRUG ADMINISTRATION

Adverse Experience Reporting for Drug Products

OMB Control No. 0910-0230 - Revision

SUPPORTING STATEMENT – **Part A: Justification**

1. Circumstances Making the Collection of Information Necessary

This information collection supports provisions found in sections 201, 502, 505, 701 and 760 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321, 352, 355, 371, and 379aa) governing adverse experience reporting (AER) and associated recordkeeping for Food and Drug Administration (FDA)-regulated drug products. The FDA has promulgated applicable regulations in 21 CFR §§ 310.305, 314.80, 314.81, 314.98, and 329.100 that implement the statutory requirements, identify specific content and format elements, and establish reporting and retention schedules for the required information. Postmarketing safety data collection and adverse event reporting are critical elements of FDA's monitoring of drugs. For more information, please visit https://www.fda.gov/drugs/surveillance/postmarketing-adverse-event-reporting-compliance-program. Respondents to the information collection are manufacturers, packers, distributors, and applicants of FDA-regulated drug and biologic products marketed with or without an FDA-approved application, including over-the-counter (OTC) drug products marketed without an approved application, OTC drug products marketed under the OTC Drug Monograph Review process (whether subject to a final monograph or not), and drug products marketed outside the monograph system.

As set forth in 21 CFR 310.305, manufacturers, packers, and distributors of marketed prescription drug products not the subject of a new drug application or abbreviated new drug application are required to report serious, unexpected adverse drug experiences, as well as follow-up reports, to FDA. The regulations also establish required recordkeeping and corresponding retention periods for the associated records. Regulations in 21 CFR 329.100 set forth like requirements applicable to *non*-prescription human drug products and similarly prescribe reporting content and format elements, as well as establish mandatory timeframes for the submission of required information and the retention of records.

Adverse experience reporting for products associated with drug marketing applications are governed by regulations in 21 CFR 314.80, 314.81, and 314.98. The regulations identify required reporting content and format elements, as well as establish follow-up reporting requirements and mandatory reporting schedules. The regulations also establish associated recordkeeping and require that written procedures be developed for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA. The regulations require reporting in an electronic format that FDA can process, although temporary waivers may be granted on a limited basis for good cause.

For efficiency of agency operations, we have revised the information collection to include burden we attribute to reporting and recordkeeping discussed in the following agency guidance documents:

- *Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application* (July 2009), implements section 760 (e) of the FD&C Act (21 U.S.C. 379aa(e)). Section 760 requires that responsible persons maintain records of nonprescription adverse event reports, whether or not the event is serious, for a period of 6 years. The guidance explains that respondents maintain records of efforts to obtain the minimum data elements for a report of a serious adverse drug event and any follow-up reports. The information collection associated with the guidance document was previously approved under OMB Control No. 0910-0636.

- *Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic* (May 2020), also pertains to postmarket reporting under section 760 of the FD&C Act. Information collection associated with the guidance document was previously approved under OMB Control No. 0910-0701.

- *Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)* (November 2016), describes the conditions under which applicants may use the International Council for Harmonisation (ICH)3 E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER) format for certain types of reporting. Information collection associated with the guidance document was previously approved under OMB Control No. 0910-0771.

We therefore request OMB approval of the information collection associated with adverse event reporting requirements found in the applicable regulations and discussed in the associated agency guidance documents.

2. Purpose and Use of the Information Collection

The information collection is intended to implement statutory requirements governing the protection of public health by facilitating the identification of FDA-regulated products that may pose a particular health risk to consumers. The requirements are intended to signal potentially serious safety problems, focusing especially on newly marketed drugs and biological products. Although premarket testing discloses a general safety profile of a product's comparatively common adverse effects, the larger and more diverse patient population exposed to the marketed product 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 information collection is required electronically in a format FDA can process. On a limited basis and for good cause, a temporary waiver may be granted from the electronic reporting requirements. We have established and maintain the FDA Adverse Event Reporting System (FAERS) at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions. Information may be submitted via FDA's Electronic Submissions Gateway (ESG) or utilizing the "*Safety Reporting Portal* (SRP)," developed by FDA and NIH to streamline reporting and review of adverse events.. The SRP was also developed as part of our MedWatch program strategic efforts.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection. Adverse experience reporting applicable to biological products is approved under OMB Control No. 0910-0308. We also maintain OMB Control Nos. 0910-0291 and 0910-0645 for paper-based and electronic reporting, respectively, through our MedWatch program

5. Impact on Small Businesses or Other Small Entities

The information collection poses no undue burden on small entities. Temporary waivers from electronic reporting requirements may be granted on a limited basis and for good cause. We assist small business through resources available on our website at https://www.fda.gov/industry/small-business-assistance.

6. Consequences of Collecting the Information Less Frequently

The information collection schedule is consistent with statutory and regulatory requirements.

7. Special Circumstances Relating to the Guidelines of 5 C.F.R. § 1320.5

Under 21 CFR § 310.305, the reporting of serious unexpected adverse drug experiences and follow up reports are required 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 the adverse experience reports are likely to reveal serious public health safety problems with the product and, thus, potentially can result in the need for expedited agency action.

The regulation requires retention of records for a period of 10 years. This retention period helps ensure that 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 only after multiple years of marketing experience.

Under 21 CFR §§ 314.80 an NDA applicant is required to notify FDA of any unexpected adverse experiences within 15 working days of receipt of information on such a reaction by the sponsor. As noted above, this shorter time for reporting is necessary so that FDA is informed as soon as possible of any serious problems with a product, so that the agency can take appropriate action. The maintenance period for retaining these records is 10 years. This extended period is due to the potential litigation, matters of public safety due to possible drug interactions in addition to the adverse experiences and need for studies of delayed effects such as carcinogenicity.

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

In accordance with 5 CFR 1320.8(d), we published a 60-day notice inviting public comment on the described information collection in the Federal Register of June 30, 2021 (86 FR 34759). No comments were received.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift is provided to respondents.

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 Questions of Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

Table 1.--Estimated Annual Reporting Burden

Authority Citation/Reference; IC Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Avg. Burden per Response	Total Hours
310.305; AER for prescription products not the subject of a marketing application	3	1	3	1	3
314.80(c)(1); 15 day alerts	5	1	5	1	5
314.80(c)(2); quarterly reports	820	17.32	14,202	60	852,120
329.100; AER for non-prescription drug products	285	690	196,650	6	1,179,900
Periodic Safety Updates; applicants w/waiver for an approved application	55	3.4	187	1	187
Periodic Safety Updates; applicants w/no waiver for an approved application	29	2.3	67	2	134
AER During Pandemic; notifying FDA when normal reporting is not feasible	350	1	350	8	2,800
Total			211,464		2,035,149

Table 2.--Estimated Annual Recordkeeping Burden

Authority Citation/Reference; IC Activity	No. of Recordkeepers	Records per Recordkeeper	Total Annual Records	Avg. Burden per Recordkeeping	Total Hours
310.305; AER records – prescription products not the subject of a marketing application	25	1	25	16	400
314.80(j); AER records – products associated w/marketing application	352	1870	658,240	16	10,531,840
FD&C Act sec.760(e)(1); GFI: *Postmarket AER for Nonprescription Drug Products* (329.100)	300	885.6667	265,700	8	2,125,600
AER During Pandemic; Continuity of Operations Planning	100	1	100	50	5,000
AER During Pandemic; documenting conditions and resultant high absenteeism	350	1	350	8	2,800
AER During Pandemic; documenting AER process	350	1	350	8	2,800
Total			924,765		0

Section 310.305(c)(5) pertains to the submission of follow-up reports to reports forwarded to the manufacturers, packers, and distributors by FDA. Under § 310.305(g), each manufacturer, packer, and distributor shall maintain for 10 years records of all adverse drug experiences required to be reported.

Applicants who have received marketing approval for drug products are required to report serious, unexpected adverse drug experiences (15-day "Alert reports"), as well as follow-up reports (§ 314.80(c)(1)) to FDA. 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 nonapplicants.

Under § 314.80(c)(2), applicants must provide periodic reports of adverse drug experiences. For the reporting interval, a periodic report includes reports of serious, expected adverse drug experiences, all nonserious adverse drug experiences, and an index of these reports; a narrative summary and analysis of adverse drug experiences; an analysis of the 15-day Alert reports submitted during the reporting interval; and a history of actions taken because of adverse drug experiences.

Under § 314.80(j), 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 (NDAs) or abbreviated new drug applications (ANDAs), manufacturers, packers, and distributors are required to report to FDA serious, unexpected adverse drug experiences as well as follow-up reports (§ 310.305(c)).

Section 760 of the FD&C Act (21 U.S.C. 379aa) also provides for mandatory safety reporting for over-the-counter (OTC) human drug products not subject to applications approved under section 505 of the FD&C Act (21 U.S.C. 355) (NDAs or ANDAs). These requirements apply to all OTC drug products marketed without an approved application, including those marketed under the OTC Drug Monograph Review process (whether or not subject to a final monograph), those marketed outside the monograph system, and including those that have been discontinued from marketing but for which a report of an adverse event was received. Under 21 CFR 329.100, respondents must submit reports according to section 760 of the FD&C Act in an electronic format.

Section 760(e) of the FD&C Act also requires that responsible persons maintain records of nonprescription drug adverse event reports, whether the event is serious or not, for a period of 6 years. FDA's guidance recommends that respondents maintain records of efforts to obtain the minimum data elements for a report of a serious adverse drug event and any follow-up reports.

We include burden we attribute to reporting and recordkeeping discussed in the guidance document, "*Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report*)," available at https://www.fda.gov/media/85520/download. The guidance describes the conditions under which applicants may use the ICH3 E2C(R2) Periodic Benefit-Risk Evaluation Report format for certain types of adverse event reporting. FDA regulations in §§ 314.80(c)(2) and 600.80(c)(2) (21 CFR 600.80(c)(2)) require applicants to submit postmarketing periodic safety reports for each approved application. The reports must be submitted quarterly for the first 3 years following the U.S. approval date and annually thereafter and must contain the information described in §§ 314.80(c)(2)(ii) and 600.80(c)(2)(ii) (the information collection associated with 21 CFR part 600--*Biological Products*, is approved under OMB control number 0910-0308).

To address concerns raised by the COVID-19 Public Health Emergency, we revised the guidance document, "*Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic*," available at https://www.fda.gov/media/72498/download. The guidance now provides recommendations pertaining to reporting and recordkeeping applicable to any pandemic, not just influenza. The guidance document includes recommendations for planning, submitting notices, and documenting continuity of operations.

12b. Annualized Cost Estimate

We assume annual administrative costs of $25,000 for maintaining toll-free telephone numbers and other portals that enable direct communications from consumers.

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

There are no other annual or capital costs to respondents.

14. Annualized Cost to the Federal Government

The information collection is supported by existing resource allocations for review of new drug marketing applications.

15. Explanation for Program Changes or Adjustments

The information collection reflects both program changes and adjustments. For efficiency of agency operations we have revised the ICR to include and account for burden we attribute to reporting and recordkeeping discussed in agency guidance documents and previously approved under OMB Control Nos. 0910-0636, 0910-0701, and 0910-0771. At the same time, we adjusted our estimates to reflect fewer reports for nonprescription drug products, which results in an overall decrease to the information collection by 2,871 hours and 218,708 responses annually.

16. Plans for Tabulation and Publication and Project Time Schedule

FDA has no such plans for the information collection.

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

As required by the PRA and consistent with established agency practice, FDA will publish a notice in the Federal Register announcing OMB approval of information collection associated with guidance documents included in this information collection. The notice will inform respondents of the OMB control number and current expiration date. However, because agency guidance documents are more frequently being accessed electronically, we are making technological updates to display the expiration date by linking to approval information found at https://www.reginfo.gov/public/. We intend to include the OMB control number and expiration date on the guidance document landing page, allowing those who download the document an easily identifiable option to view this information. This also allows the agency to more easily update the expiration date upon renewal and/or revision of OMB approval of associated information collection. We are taking this approach to improve compatibility with current website platforms utilized by FDA.

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18. Exception to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.