UNITED STATES FOOD & DRUG ADMINISTRATION

Animal Drug Adverse Event Reporting and Recordkeeping

OMB Control No. 0910-0284
RIN 0910-AH51

SUPPORTING STATEMENT – **Part A: Justification**

1. Circumstances Making the Collection of Information Necessary

This information collection request supports rulemaking. With regard to adverse events and product/manufacturing defects associated with approved new animal drugs, section 512(l) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360b(l)) requires applicants with approved new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs) to establish and maintain records and reports of data relating to experience with uses of such drug, or with respect to animal feeds bearing or containing such drug, to facilitate a determination under section 512(e) as to whether there may be grounds for suspending or withdrawing approval of the NADA or ANADA under section 512(e) or 512(m)(4). FDA is issuing this final rule to amend our regulations under § 514.80 (21 CFR 514.80) to require electronic submission of certain postmarketing safety reports for approved new animal drugs and to provide a procedure for requesting a temporary waiver of the requirement. This action will improve our systems for collecting and analyzing postmarketing safety reports. The change will help us to more rapidly review postmarketing safety reports, identify emerging safety problems, and disseminate safety information in support of our public health mission. In addition, the amendments will facilitate international harmonization and exchange of safety information.

The final rule requires electronic submission for the following reports for approved new animal drugs: 3-day alert reports that applicants elect to submit directly to FDA's Center for Veterinary Medicine (CVM) in addition to the requirement they have to submit these reports on paper Form FDA 1932 to the appropriate FDA District Office or local FDA resident post; 15-day alert reports and followup reports; product/manufacturing defect and adverse drug experience reports submitted by nonapplicants who elect to report adverse drug experiences directly to CVM in addition to providing these reports to the applicant; product/manufacturing defect and adverse drug experience reports (including reports of previously not reported adverse drug experiences that occur in postapproval studies) required to be submitted as part of the periodic drug experience report.

We therefore request OMB approval of the information collection provisions of the final rule, as discussed in this supporting statement, including one-time recordkeeping burden for creating new SOPs to submit the reports electronically and the one-time burden of training employees to electronically submit postmarketing safety reports to CVM in accordance with the new SOPs.

2. Purpose and Use of the Information Collection

The purpose of this information collection is to enable the submission and review of certain postmarketing safety reports for approved new animal drugs. This rule does not change the content of these postmarketing safety reports or the frequency of the reporting requirements.

Section 514.80 requires applicants and nonapplicants to keep records of and report to us data, studies, and other information concerning experience with new animal drugs for each approved NADA and ANADA. Following complaints from animal owners or veterinarians, or following their own detection of a problem, applicants or nonapplicants are required to submit adverse event reports and product/manufacturing defect reports under § 514.80(b)(1), (b)(2)(i) and (ii), (b)(3), and (b)(4)(iv)(A) and (C) on Form FDA 1932.

We review the records and reports required in § 514.80 to facilitate a determination under section 512(e) of the FD&C Act as to whether there may be grounds for suspending or withdrawing approval of the new animal drug.

The final rule also revises these requirements to allow applicants or nonapplicants to request a temporary waiver from the electronic submission requirement for "good cause" shown. Examples of circumstances that could constitute "good cause" for granting waivers of the electronic submission requirement include crisis situations that impact an applicant's or nonapplicant's ability to report electronically, such as natural disasters, pandemics, and terrorism. The rule requires applicants and nonapplicants to submit a waiver request to us in writing. The initial request, however, could be made by telephone or email to CVM's Division of Veterinary Product Safety, with prompt written followup submitted as a letter to the application. We will use the information sent to us in a waiver request to make a determination to allow a temporary waiver of the electronic submission requirement.

The continuous monitoring of new animal drugs affords the primary means by which we obtain information regarding problems with the safety and efficacy of marketed approved new animal drugs, as well as product/manufacturing problems. Postapproval marketing surveillance is important to ensure the continued safety and effectiveness of new animal drugs. Drug effects can change over time and other effects may not manifest until years after the approval.

Description of Respondents: Respondents to this collection of information are applicants and nonapplicants. An applicant is defined as "a person or entity who owns or holds on behalf of the owner the approval for an NADA (new animal drug application) or an ANADA (abbreviated new animal drug application), and is responsible for compliance with applicable provisions of the act and regulations." (§ 514.3 (21 CFR 514.3)) In addition, nonapplicants, defined in § 514.3 as "any person other than the applicant whose name appears on the label and who is engaged in manufacturing, packing, distribution, or labeling of the product," may elect to submit adverse drug experience reports directly to

us (§ 514.80(b)(3)). Respondents include individuals and the private sector (for-profit businesses).

3. Use of Improved Information Technology and Burden Reduction

Currently, most submitters have chosen, voluntarily, to use electronic submission for the reports affected by this final rule. As of 2016, approximately 99.7 percent of postmarketing safety reports eligible for electronic submission were electronically submitted. Thus, this final rule will affect a small proportion of these reports.

Electronic reports may be submitted through FDA's Electronic Submission Gateway or through the FDA-National Institutes of Health Safety Reporting Portal (Safety Reporting Portal). The Electronic Submission Gateway allows applicants or nonapplicants to submit postmarketing safety reports using the Health Level 7 (HL7) Individual Case Safety Report (ICSR)standard that has been adopted worldwide by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). In this final rule, we reaffirm our intention to continue to rely on these VICH-recommended standards. We believe the continued use of VICH standards will promote harmonization of safety reporting among regulatory agencies and facilitate the international exchange of postmarketing safety information. Accordingly, this final rule is consistent with our ongoing initiatives to encourage the widest possible use of electronic submission and to promote international harmonization of safety reporting for animal drug products through reliance on VICH standards. We anticipate that the final rule will enhance industry's global pharmacovigilance practices by allowing it to use common data elements and transmission standards when submitting ICSRs to multiple regulators. The Electronic Submission Gateway provides industry with gateway-to-gateway access to transmit an HL7 ICSR message using the FDA electronic submission standard. The Safety Reporting Portal provides applicants or nonapplicants a means to submit individual postmarketing safety reports without having to make financial investments in the technical infrastructure needed to access the Electronic Submission Gateway. Any person who has internet access can use the Safety Reporting Portal to submit reports through a user-friendly, interactive questionnaire available at https://www.safetyreporting.hhs.gov/.

Burden for the electronic version of Forms FDA 1932 and 1932a is accounted for under OMB control number 0910-0645. FDA anticipates over time that adverse event reporting for small businesses will shift more and more to the electronic FDA Safety Reporting Portal.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection.

5. Impact on Small Businesses or Other Small Entities

We estimate that ten percent 10% of respondents are small businesses. Although new animal drug development is typically an activity completed by large drug firms, the information collection required under 21 CFR 514.80 applies to small as well as large companies. As noted, electronic reports may be submitted through FDA's Electronic Submission Gateway or through the Safety Reporting Portal. The Safety Reporting Portal provides applicants or nonapplicants, which may be small businesses, a means to submit individual postmarketing safety reports without having to make financial investments in the technical infrastructure needed to access the Electronic Submission Gateway. Any person who has internet access can use the Safety Reporting Portal to submit reports through a user-friendly, interactive questionnaire available at https://www.safetyreporting.hhs.gov/. For applicants or nonapplicants that submit a small number of reports, the use of the web-based Safety Reporting Portal may be more cost effective than implementing a system to send an HL7 ICSR message through the FDA Electronic Submission Gateway.

Under the Regulatory Flexibility Act, CVM analyzes regulatory options that would minimize any significant impact on small entities. FDA aids small businesses in complying with its requirements through the agency's Regional Small Business Representatives and through the scientific and administrative staffs within the agency. FDA has provided a Small Business Guide on the agency's website at http://www.fda.gov/ForIndustry/SmallBusinessAssistance/default.htm.

6. Consequences of Collecting the Information Less Frequently

Data collection schedule occurs occasionally and is consistent with statutory and regulatory requirements. Less frequent data collection would hinder early detection of such threats to the public health. New, unusual, and serious adverse events can appear at any time due to the large distribution of the drug as compared to its use during the preapproval clinical trials.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The reporting requirements under 21 CFR 514.80 are inconsistent with 5 CFR 1320.5. This section requires justification for requesting respondents to report more often than quarterly. Pursuant to 21 CFR 514.80(b)(1), the applicant is required to submit product and manufacturing defects that may result in serious adverse drug events within 3 working days of first becoming aware that a defect may exist. Pursuant to 21 CFR 514.80(b)(2)(i)-(ii), the applicant is required to submit initial and follow-up reports within 15 working days. Pursuant to 21 CFR 514.80(b)(3), the non-applicant required to report adverse drug experiences to the applicant within 3 working days of first receiving the information or if reported to FDA within 15 working days. This short time for reporting is necessary to inform us as soon as possible of any serious problems with a drug product, so that we can take appropriate action.

The maintenance period for keeping records is also inconsistent with 5 CFR 1320.6. Pursuant to 21 CFR 514.80(e), the applicant and non-applicant must maintain records and reports of all information for a period of 5 years after the date of submission. This extended period is due to the potential for litigation, delayed recognition of adverse drug experiences, long expiration dates, and needed for studies of delayed effects such as carcinogenicity.

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

As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995 (PRA), we provided an opportunity for public comment on the information collection requirements of the proposed rule that published in the Federal Register of February 14, 2018 (83 FR 6480). The comments we received and our responses are discussed in the final rule as well as here:

(Comment 1) Comments from a drug manufacturing firm, as well as an individual, generally support our efforts to require electronic submission of certain postmarketing safety reports for approved new animal drugs. One comment recognizes that the requirement of electronic submission would greatly benefit the Agency and animal health by supporting quicker access to postmarketing safety information. Another comment applauds our efforts to improve our systems for collecting and analyzing postmarketing safety reports and to facilitate international harmonization and exchange of safety information.

(Response 1) We appreciate the general support that the comments express. As noted in section II.A., we expect this rule to expedite our access to safety information and provide us data in a format that will support more efficient and comprehensive reviews. This will enhance our ability to rapidly communicate information about suspected problems to animal owners, veterinarians, consumers, and industry within the United States and internationally in support of our public health mission.

(Comment 2) One comment states that, although in favor of electronically reporting 3-day alerts to CVM in addition to reporting to the appropriate FDA District Office or local resident post, until such time that this can be accomplished via a single mechanism (i.e., electronic reporting to both segments of the Agency simultaneously), this places an undue burden on industry both in time and resources as this would require reporting electronically to CVM while continuing to file paper Form FDA 1932 to District Offices or local resident posts.

(Response 2) We currently require 3-day alert reports to be submitted to the appropriate FDA District Office or local FDA resident post on paper. (See § 514.80(b)(1)) However, if in addition to that report an applicant elects to submit a 3-day field alert report directly to CVM (i.e., a "courtesy copy"), we proposed to require the applicant to submit that additional copy of the report to CVM electronically. (See proposed 514.80(b)(1)) At this time FDA District Offices do not have the technology to receive Form FDA 1932

electronically, so we cannot mandate electronic reporting to FDA District Offices at this time. In addition, the FDA District Offices and local FDA resident posts use a different database for tracking such reports, and do not have direct access to the CVM Adverse Drug Event (ADE) database (which receives ADE information in part from Form FDA 1932). We agree that development of a single mechanism to report 3-day alert reports via electronic Form FDA 1932 to both the FDA District Office (or local FDA resident post) and CVM is ideal, and we are interested in developing this capacity; however, this effort is preliminary and investigatory at this time. As there is currently no requirement to provide a "courtesy copy" of 3-day alert reports to CVM, the required electronic submission of such copies would only burden those applicants that choose to provide them despite any additional time and resources needed to do so. Therefore, in this final rule, we are keeping the language of the final rule as proposed at § 514.80(b)(1).

(Comment 3) One comment notes that, since the implementation of electronic reporting capability, postmarketing safety reports may be submitted to us via Extensible Markup Language (XML), which is designed to store and transport data and be both human-readable and machine-readable. Therefore, there is no official Form FDA 1932 version of these reports to provide to an inspector during manufacturing site FDA inspections. In addition, the comment continues, inspectors are not well versed in reading the XML formats created from electronically submitted reports. The comment suggests that we provide training to inspectors to help them better understand how to read the XML format for case data or that we provide industry with guidance for an alternative form that could be generated from the database that satisfies the inspectors' needs during site inspections.

(Response 3) We recognize the comment's concerns with regard to utility of the XML format information during inspections. We appreciate the commenter's interest in either preparing more easily readable versions of electronically submitted reports for inspectors or providing training to inspectors in reading the XML format of electronically submitted reports. We intend to consider these suggestions so that inspectors are better able to access the information they need during an inspection. However, the comment did not request any changes to the language in proposed § 514.80(b)(1), nor do we see a reason to make any changes based on the concerns and suggestions included in the comment.

(Comment 4) One comment notes that, while the proposed rule provides a procedure for requesting a temporary waiver of the electronic submission requirement for "good cause" (i.e., crisis situations that impact an applicant's or nonapplicant's ability to report electronically, such as natural disasters, pandemics, and terrorism), the proposed rule does not change the content, frequency, or timeline for submission of the postmarketing safety reports to the Agency. The comment suggests that, when the Agency's Electronic Submission Gateway or Safety Reporting Portal is down, we should grant a temporary waiver of the electronic submission requirement for a period of time (e.g., for the length of time that the Agency website/portal is down.)

(Response 4) In the proposed rule, we described that an applicant or nonapplicant experiencing technical difficulty that temporarily prevents use of the Electronic Submission Gateway could, as a backup, electronically submit reports using the Safety

Reporting Portal. An applicant or nonapplicant that relies on the Safety Reporting Portal but experiences a short-term, temporary interruption of internet services could, as a backup, electronically submit reports from any other computer with access to a working internet connection. We anticipate that temporary waivers of the electronic submission requirement will only be needed in rare circumstances such as natural disasters, pandemics, etc. In addition, we discussed in the preamble that in the unlikely event that the Agency experiences a prolonged system outage or other major technical problem, we may require an applicant or nonapplicant to submit reports that would otherwise be required to be submitted electronically to be submitted in an alternate format (most likely on paper using Form FDA 1932 (83 FR 6480 at 6485). We are not waiving the required content, frequency, or timeline for submission of the postmarketing safety reports to the Agency; applicants and nonapplicants should be prepared to comply with an Agency request for submission in an alternate format by maintaining the capability to submit paper reports using Form FDA 1932 if needed. We are finalizing proposed 514.80(d) without change.

9. Explanation of Any Payment or Gift to Respondents

There are no payments or gifts to respondents.

10. Assurance of Confidentiality Provided to Respondents

In preparing this Supporting Statement, our FDA Privacy Office was consulted to ensure appropriate handling of information collected. This Information Collection Request (ICR) is collecting personally identifiable information (PII) in the context of the individuals' professional capacity. This affects certain reports submitted on Form FDA 1932. The PII submitted for Form FDA 1932 (*Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report*) is name, company name, company address, telephone number, fax number, and email address. This ICR involves reporting adverse events and product/manufacturing defects associated with approved new animal drugs. Although PII is collected, the collection is not subject to the Privacy Act of 1974 and the particular notice and other requirements of the Act do not apply. Specifically, FDA does not use name or any other personal identifier to routinely retrieve records from the information collected. FDA also minimized the PII to be collected to protect the privacy of the individuals.

We expect that regulatory information will contain trade secret and commercial confidential information. As a result, all files are maintained in a secured area. Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 514.11. Only information that is releasable under the agency's regulations in 21 CFR part 20 would be released to the public. This information is also safeguarded by section 301(j) of the FD&C Act and would be protected from disclosure under the Freedom of Information Act (FOIA) under sections 552(a) and (b) (5 U.S.C. 552(a) and (b)). Further, under the terms of the Freedom of Information Act, the veterinarian's name, address, and phone number, and the owner's name, etc., reported on Form FDA 1932 cannot be made available to a public request. To the extent 21 CFR

20.64 applies, we will honor the confidentiality of any data in investigation records compiled for law enforcement purposes.

11. Justification for Sensitive Questions

This information does not contain questions pertaining to sex behavior, attitude, religious beliefs, or any other matter commonly considered private or of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

Table 1.--Estimated Recurring Reporting Burden[1]

21 CFR Section	Form FDA No.	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Electronic submission of postmarketing safety reports under § 514.80(b)(1), (b)(2)(i) and (ii), (b)(3), and (b)(4)(iv)(A) and (C)	1932	15	18	270	1	270
Request for waiver, § 514.80(d)(2)	N/A	1	1	1	1	1
Total				271		271

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

Table 1 reflects the recurring reporting burden we estimate is associated with the final rule. Consistent with section II.F. of the *Final Regulatory Impact Analysis (FRIA)*, we estimate that 15 firms submitted a paper Form FDA 1932 report from 2011 to 2015 and thus will be affected by the rule's requirement to submit electronically. As stated in the FRIA, we estimate that in 2016 CVM received 270 of the affected postmarketing safety reports on paper. We calculate the number of responses per respondent as the total annual responses divided by the number of respondents. We assume that, on average, it will take 1 hour to submit electronic postmarketing safety reports for approved new animal drugs, for a total of 270 hours. We base our estimate of 1 hour per report on our experience with electronic postmarketing safety reporting. In the FRIA, we also estimate the burdens associated with submission of waiver requests. We expect very few waiver requests (see section II.F.2. of the FRIA), estimating that approximately one firm will request a waiver annually under § 514.80(d)(2). We assume a waiver request takes 1 hour to prepare and submit. Together, this results in a total of 271 hours and 271 responses. We have also added 1 hour to the paper reporting collection to reflect the new waiver request process under § 514.80(d)(2).

Table 2.--Estimated One-Time Recordkeeping Burden[1]

Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Write New SOPs	15	1	15	20	300
Training	15	1	15	20	300
Total			30		600

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

Table 2 reflects one-time recordkeeping burden we estimate is associated with the final rule. This burden includes both the one-time burden of creating new SOPs to submit the reports electronically and the one-time cost of training employees to electronically submit postmarketing safety reports to CVM in accordance with the new SOPs. In section II.F. of the FRIA, we estimated that approximately 15 firms will be affected by this rule. We also estimated that it will take approximately 20 hours per firm to create new SOPs for electronic submission of postmarketing safety reports and approximately 20 hours per firm to complete the training of employees to electronically submit postmarketing safety reports in accordance with the new SOPs. Together, this results in a total of 600 hours and 30 records. We assume that there are no capital costs associated with firms implementing this rule (i.e., applicants and nonapplicants in the pharmaceutical industry already have the computer and internet capacity necessary to electronically submit postmarketing safety reports).

12b. Annualized Cost Burden Estimate

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Industry Compliance Officer	871	$51.75	$45,074.25

[1] May 2018 National Industry-Specific Occupational Employment and Wage Estimates, Bureau of Labor Statistics and including 30% for benefits (https://www.bls.gov/oes/current/naics4_325400.htm).

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

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

Costs to the Federal Government are absorbed through existing resource allocations.

15. Explanation for Program Changes or Adjustments

This rulemaking revises the information collection to require electronic reporting or the granting of a waiver from the requirement. We have updated our mandatory reporting element (IC element 1) to reflect estimates consistent with the final rule, which results in

a decrease in both annual responses and burden hours in the amount of 1512. This is because the currently approved estimate was shown to be too high by the FRIA for the final rule. Ultimately, upon approval of the revision, the 270 responses and hours attributable to mandatory electronic reporting will be captured under OMB Control No. 0910-0645, FDA's Adverse Event Reporting System (which administers our MedWatch Program), however the 1 request for waiver will be retained in this information collection. We have also added a one-time recordkeeping burden in the amount of 30 responses and 30 burden hours to reflect implementation of the new requirements, but we expect this burden to be realized upon the next renewal request for the information collection (currently expires March 31, 2021). Cumulatively, these changes reflect a total decrease of 1481 hours and 1481 responses annually.

16. Plans for Tabulation and Publication and Project Time Schedule

No statistical reporting, tabulation, or publication of the data are planned.

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

Display of the OMB Expiration Date is appropriate.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.