

OMB Control Number 0910-0284
SUPPORTING STATEMENT

RECORDS AND REPORTS CONCERNING EXPERIENCE WITH APPROVED NEW
ANIMAL DRUGS

A. JUSTIFICATION

1. Circumstances Making the Information Collection Necessary

This final rule amends the provisions of the animal drug regulations concerning requirements for recordkeeping and reports concerning experiences to approved new animal drugs. The information contained in the reports required by this rule enables FDA to monitor the use of new animal drugs after approval and to ensure their continued safety and efficacy. The reporting requirements include: a report that provides information on product and manufacturing defects that may result in serious adverse drug events within 3 days (new Sec. 514.80(b)(1)); a report that provides information on serious and unexpected adverse drug events and a follow-up report on such events (new Sec. 514.80(b)(2)); a summary report of increased frequency of adverse drug experiences (new Sec. 514.80(b)(4)(v)); a report from nonapplicants, such as distributors, to applicants providing information on adverse drug experiences (new Sec. 514.80(b)(3)); a periodic report with information on distribution, labeling, manufacturing or controls changes, new laboratory studies, and all adverse events in the reporting period (new Sec. 514.80(b)(4)); and other reports that include special drug experience report; reports for advertising and promotional material, and reports for distributor statements (new Sec. 514.80(b)(5)). These reports must be kept for 5 years (new Sec. 514.80(e)).

The final rule strengthens the current reporting system by requiring periodic reports every 6 months for the first 2 years following initial approval of an application rather than just for the first year following initial approval. The increased burden on applicants amounts to one additional periodic report. While greater than the reporting burden in the previous rule, this burden is less than that of the proposed rule which would have required quarterly periodic reports for 3 years following initial approval.

The reporting burden of the proposed rule has been reduced further in other ways. In the final rule, only reports pertaining to product and manufacturing defects must include only information on defects “that may result in serious adverse drug events” as 3-day reports (new Sec. 514.80(b)(1)) rather than information on all manufacturing defects, as in the proposed rule. Additionally, the proposed rule required a periodic adverse drug experience report and an annual report, whereas the final rule has combined these reports into a single periodic drug experience report (new Sec. 514.80(b)(4)). The final rule also reduces the reporting requirements of the proposed rule by eliminating proposed Sec. 514.82, which required records and reports from manufacturers, packers, labelers, and distributors other than the applicant. The recordkeeping requirements of the proposed rule have also been reduced in the final rule by changing the required period of time records must be kept from 10 to 5 years (new Sec. 514.80(e)).

All periodic reports must be submitted with Form FDA 2301, “Transmittal of Periodic Reports and Promotional Materials for New Animal Drugs” (OMB Control No. 0910-0012). Adverse drug experience reports must be submitted on Form FDA 1932, and 1932a (voluntary) “Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report” (OMB Control No. 0910-0012)

The specific citations within 21 CFR 500 regarding information collection requirements for which we request OMB approval are:

21 CFR 514.80(e) Recordkeeping.

Cites requirements that an applicant and nonapplicant establish and maintain records and files containing full records of information pertinent to the safety or effectiveness of a new animal drug that have not been previously submitted as part of the application.

21 CFR 514.80(b)(1) Reporting.

Specifies information to be submitted on product defect/manufacturing defects that may result in serious adverse drug events are to be reported within 3 working days of first becoming aware that a defect may exist. A product defect/manufacturing defect is the deviation of a distributed product from the standards specified in the approved application. Specifies information to be submitted concerning significant chemical, physical or other change, or deterioration of the product; product contamination; a mix-up in a drug or its labeling; defective packaging; damage from disaster; or failure of a drug to meet established specifications.

21 CFR 514.80(b)(2)(i) Reporting.

Specifies requirements for submitting initial reports of serious adverse drug events and unexpected adverse drug events that include, but are not limited to, adverse events occurring in animals, failure of a new animal drug to produce its expected pharmacological properties or clinical effect (lack of effectiveness), and an adverse event occurring in humans from exposure to a new animal drug, all of which must be reported within 15 working days of first receiving the information.

21 CFR 514.80(b)(2)(ii) Reporting.

Specifies requirements for submitting follow-up reports to the initial report of serious adverse drug events and unexpected adverse drug events.

21 CFR 514.80(b)(2)(iii) Reporting.

Specifies requirements for periodically reviewing the incidence of reports of adverse drug experiences to

determine an increase in frequency of serious (expected and unexpected) adverse drug events. Specifies the information and format to be submitted.

21 CFR 514.80(b)(3) Reporting.

Specifies requirements by nonapplicants to forward reports of adverse drug events to the applicant within 3 working days of first receiving the information. Nonapplicants may also elect to submit reports directly to FDA within 15 working days of first receiving the information.

21 CFR 514.80(b)(4)(i)-(iv) Reporting

Specifies requirements for submitting 6 month periodic drug experience reports for first two years following approval and then yearly thereafter. Specifies for yearly drug experience reports that applicants may petition FDA to change the date of reporting and(or) the frequency of reporting. Specifies requirements for submitting distribution data for each new animal drug product for quantities distributed domestically and quantities exported; applicant and distributor current package labeling; nonclinical laboratory studies and clinical data not previously reported; and adverse drug experiences not previously submitted in the periodic drug experience reports.

21 CFR 514.80(b)(5)(i) Reporting

Specifies requirements for submitting special drug experience reports at different times or more frequently from those stated in 21 CFR 514.80.

21 CFR 514.80(b)(5)(ii) Reporting

Specifies requirements for submitting advertisements and promotional labeling.

21 CFR 514.80(b)(5)(iii) Reporting

Specifies requirements for submitting distributor statements.

2. Purpose and Use of the Information

The information obtained for 21 CFR 514.80(b)(1) on product and manufacturing defects may originate from an owner of an animal, a veterinarian, a nonapplicant, or the applicant. The applicant is then required to report the episode to the Food and Drug Administration on the Form FDA 1932.

Monitoring for product and manufacturing defects is an essential part of the FDA's regulatory mission. These product and manufacturing defect reports are used by CVM as a primary means of obtaining information regarding potential product and manufacturing problems with specific lots of marketed animal drug products. Reports from veterinarians and others are essential because there is no other effective way of obtaining this needed information. The reports are reviewed to identify any potential

violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). If a violation of the FD&C Act appears to exist, the report is followed up with an assignment memorandum to the appropriate FDA field office requesting a limited inspection of the firm to gather more facts and needed evidence in support of a product recall or regulatory action such as seizure or injunction. Alternatively, when the drug is the subject of a new animal drug application (NADA) the sponsor may be asked to investigate the cause and effect of the product defect and supplement their NADA to provide for appropriate changes in the manufacturing control section of the NADA.

The information obtained for 21 CFR 514.80(b)(2) may originate from an owner of an animal, who registers a complaint with the applicant, who is then required to report the episode to the Food and Drug Administration on the Form FDA 1932. Alternatively, the information obtained for 21 CFR 514.80(b)(3) may originate from an owner of an animal, who registers a complaint with the nonapplicant, who registers a complaint with the applicant, who is then required to report the episode to the Food and Drug Administration on the FDA Form 1932. Further, the safety and effectiveness of monitoring activities involving drug products also relies on voluntary reports of suspected drug effects, or drug ineffectiveness complaints from practicing veterinarians or animal owners. These reports are usually submitted directly to FDA, Center for Veterinary Medicine, on Form FDA 1932a, a short, convenient, easily completed form. The product that is the subject of the complaint may be either an over-the-counter product (available to anyone), or it may be a prescription product (available only to or by order of a veterinarian). In either case, the name of the owner of the animal(s) is germane to the identification of the episode in order that a specific reaction not be counted twice. The safety and effectiveness of monitoring activities involving drug products also relies on voluntary reports of suspected drug effects, or drug ineffectiveness complaints from practicing veterinarians. The reports are reviewed by an FDA Veterinary Medical Officer to determine the probability that the drug caused the adverse effect, or that the drug was ineffective. After the individual report is reviewed, it is added to Division of Surveillance's Adverse Drug Experience (ADE) computer database file containing other previously reported ADE data for that drug. Applicants are being required to periodically review their incidences of adverse drug experiences to determine if any changes in the specific product or labeling are needed. Careful evaluation sometimes leads to label or package insert changes, dosage changes, additional warnings or contraindications, product reformulation, or on rare occasions withdrawal of the approved new animal drug application.

The information obtained for 21 CFR 514.80(b)(4) may originate from a nonapplicant, who reports the information to the applicant, who is then required to report to the Food and Drug Administration accompanied with Form FDA 2301. The applicant is required to submit reports every 6 months for the first two years following approval of an ANADA or NADA and yearly thereafter. The applicant must submit distribution data; labeling for both applicant and distributor; description of manufacturing and control changes; non-clinical laboratory studies and clinical data not previously reported, and adverse drug experiences not previously reported under 21 CFR 514.80(b)(1) and (b)(2). The applicant must report to the FDA all reports of information from any source pertinent to the safety and effectiveness of the new animal drug for the purpose of determining whether there are grounds for withdrawing or suspending approval. The information undergoes a full and comprehensive review by FDA scientists to

evaluate the impact and significance of reported manufacturing and control changes, and non-clinical laboratory studies and clinical data on the safety and effectiveness of the product. Labeling is reviewed for accuracy of claims, directions for use and general compliance with the Act and regulations. Adverse drug experiences undergo the aforementioned review (21 CFR 514.80(b)(1) and (b)(2)). The distribution data are reviewed to determine eminency of product shortages, and availability for bioterrorism issues. Upon determination of a product shortage, a review of the distribution data for other products will indicate alternate therapeutic products to be used.

The information obtained for 21 CFR 514.80(b)(5)(ii) may originate from a nonapplicant, who reports the information to the applicant, who is then required to report to the Food and Drug Administration accompanied by a completed Form FDA 2301. The applicant must submit mailing pieces and other labeling for prescription and over-the-counter new animal drugs at the time of initial dissemination. For prescription animal drugs, the applicant must submit advertisements at the time of initial publication or broadcast. The information is reviewed by a CVM scientist for accuracy of claims, fair balance of safety and effectiveness information, and general compliance with the Act and regulations.

The information obtained for 21 CFR 514.80(b)(5)(iii) originates from a nonapplicant, who reports the information with the applicant, who is then required to report to the Food and Drug Administration accompanied by a completed Form FDA 2301. The applicant must submit the current product labeling for both the applicant and distributor. Additionally, a signed statement from the distributor must be completed. The labeling for the applicant and distributor must be identical except for a different and suitable proprietary name, and the name and address of the distributor. The name and address of the distributor must be preceded by an appropriate qualifying phrase such as “manufactured for” or “distributed by” or as specified in other regulations. The labeling is for accuracy as mentioned above and for general compliance with the Act and regulations. The distributor states the following in distributor statement: 1) the category of their operation (e.g., wholesale or retail), 2) that they will distribute the new animal drug only under the approved labeling, 3) that they will advertise the product only for use under the conditions stated in the approved labeling, 4) that they will adhere to the records and reports requirements of 21 CFR 514.80, and 5) that they are regularly and lawfully engaged in the distribution or dispensing of prescription products if the product is a prescription new animal drug.

If the collection of information were not conducted, there would be no continuous monitoring of the safety and effectiveness of marketed animal drugs. Data already on file with CVM are not adequate because new animal drugs are continually being approved, drug effects can change over time, and less apparent effects sometimes take a number of years to detect.

3. Use of Information Technology and Burden Reduction

Many of the applicants have automated systems for reports of adverse drug experiences to new animal drugs. CVM has provided under 21 CFR 514.80(d) that applicants may computer generate Form FDA 1932 or Form FDA 2301. CVM is working domestically with the animal pharmaceutical industry

and internationally under VICH to develop methods and standards for electronic submissions of adverse drug experiences. Also, CVM is working on revising the FDA Form 2301 to allow for electronic submission of the Periodic Drug Experience Reports, which includes amount of drug marketed, adverse drug experiences, advertisement and promotional information, and other information.

4. Efforts to Identify Duplication and Use of Similar Information

This information is not collected by any other agency in the Government. The information collection required as a result of 21 CFR 514.80 does not duplicate any other information collection.

5. Impact on Small Business or Other Small Entities

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. However, under the Regulatory Flexibility Act, CVM analyzes regulatory options that would minimize any significant impact on small entities. CVM will assist small businesses in complying with regulatory requirements. FDA will provide help to small firms through the Office of Small Manufacturers Assistance, if requested. This regulation is not expected to have a significant economic impact on these small entities since the final rule is intended to simplify and clarify current recordkeeping and reporting requirements.

6. Consequences of Collecting the Information Less Frequently

Part 514.80 establishes a reporting frequency that is dictated by the need to focus on potential problems concerning the safety and effectiveness of new animal drugs. Less frequent data collection would hinder early detection of such threats to the public health. New, unusual, and serious adverse experiences can suddenly begin to appear due to many reasons and under many circumstances. Also, when a new drug is approved, adverse reactions 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(b)(1), (b)(2)(i)-(ii), (b)(3), and (e) 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 report 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 nonapplicant is 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 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 records is also inconsistent with 5 CFR 1320.6. Pursuant to 21 CFR 514.80(e), the applicant and nonapplicant 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 of litigation, 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 Agency

In the Federal Register of February 4, 2002 (67 FR 5046), FDA invited comments on the interim final rule and the information collection requirements. Only one comment received pertained to information collection. The commenter stated that the requirements under “Multiple Applications” do not appear to decrease but may increase the burden on the applicant. In particular, the comment questioned the requirement under §514.80(c)(4) and requested clarification. The comment also voiced concern about an increased reporting burden due to the increasing number of approved combinations of drugs for use in feeds since the implementation of the Animal Drug Availability Act of 1996. Further complicating the reporting issue is that frequently there are nonapplicants involved in the marketing of these combinations. The comment stated that with the exception of “promotional literature,” there is rarely any other information to be reported. The comment suggested that the “promotional literature” be submitted to the application held by either party, i.e., the nonapplicants or applicant, and not the application approved for the use of the combination of drugs.

In response, FDA notes that the provision of the regulation in question is currently codified under §510.300(b)(4)(ii). The current regulation and the proposal in the interim final rule are similar. There is no increase of the reporting burden. It is not the intention of FDA for the implementation of §514.80(c) to be different from the current requirement under §510.300(b)(4)(ii). There is no additional reporting burden than that already covered under §514.80(b)(4). Section 514.80(c) is not additional information collection, i.e., in addition to §514.80(b)(4); it is an administrative tool for industry to use to submit common information only once to FDA. Only information specific to a particular NADA/ANADA that is not common to all the applications must be included in the report for that particular NADA/ANADA; for example, labeling. With regard to the comment that there is an increased reporting burden due to the Animal Drug Availability Act of 1996, increased reporting is due to the increased number of approved applications. FDA consequently believes that this is a reasonable reporting requirement.

9. Explanation of Any Payment or Gifts to Respondents

There are no payments or gifts to respondents.

10. Assurance of Confidentiality Provided to Respondent

During working hours, only FDA employees have access to the computer files and database on a need-to-know basis. During duty and non-duty hours building security is provided through a contract with a

private protection agency. None of these provisions bar the release of the confidential information if subpoenaed by a court of law. Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 514.11 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act. 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.

11. Justification for Sensitive Questions

This information does not contain questions pertaining to any matter commonly considered private or of a sensitive nature.

12. Estimates of Hour Burden Including Annualized Hourly Costs

ESTIMATED ANNUAL REPORTING BURDEN^a

21 CFR Section No./ Title/ FDA Form No.	No. of Respondents	Annual Frequency of Response	Total Annual Responses	Hours per Response	Total Hours
514.80(b)(1)/3-day field alert report/ Form FDA 1932	190	0.50	95	1	95
514.80(b)(2)(i)/original 15-day alert report/Form FDA 1932	190	64.65	12,283	1	12,283
514.80(b)(2)(ii)/follow-up 15-day alert report/Form FDA 1932	190	31.62	6,007	1	6,007
514.80(b)(2)(iii)/increased frequency 15-day alert report	190	1.58	300	2	600
514.80(b)(3)/nonapplicant report/ Form FDA 1932	340	2.94	1,000	1	1,000
514.80(b)(4)/periodic drug experience report/Form FDA 2301 ^b	190	6.45	1,226	11	13,486
514.80(b)(5)(i)/special drug experience report/Form FDA 2301	190	0.13	25	2	50
514.80(b)(5)(ii)/advertising and promotional materials report/Form FDA 2301	190	4.06	772	2	1544
514.80(b)(5)(iii)/distributor's statement report/Form FDA 2301	530	0.11	56	2	112
Total					35,177

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

^bThe reporting burden for 514.80(b)(4)(iv)(A) is included in the reporting burden for 514.80(b)(2)(i) and (c).

ESTIMATED ANNUAL RECORDKEEPING BURDEN^a

21 CFR Sect. No.	No. of Respondents	Frequency of Response	Total Annual Responses	Hours per Response	Total Hours
514.80(e) ^b	530	36.58	19,385	0.5	9,693
514.80(e) ^c	530	4.49	2,379	10.35	24,623
Total					34,316

^aBurden estimates were separated between Form FDA 1932 and Form FDA 2301 to reflect the difference in estimates for "Hours per Respondent" required.

^bRecordkeeping estimates for 514.80(b)(1), 514.80(b)(2)(i), 514.80(b)(2)(ii), and 514.80(b)(3); Form FDA 1932.

⁶Recordkeeping estimates for 514.80(b)(2)(iii), 514.80(b)(4), 514.80(c), and 514.80(b)(5); Form FDA 2301.

Forms FDA 1932 and FDA 2301 for this collection of information are currently approved under OMB Control No. 0910-0012 and will be included in the implementation of this regulation. The reporting and recordkeeping burden estimates in this Federal Register document are based on the submission of reports to the Division of Surveillance, Center for Veterinary Medicine. The total annual response numbers are based on the 2000 fiscal year submission of reports to the Division of Surveillance, Center for Veterinary Medicine. The annual frequency of response was calculated as the total annual responses divided by the number of respondents.

Form FDA 1932a for this collection of information is currently approved under OMB Control No. 0910-0012 and will be included in the implementation of this regulation. An estimated 100 responses from individual veterinarians are voluntarily submitted directly to FDA on Form FDA-1932a each year. This voluntary reporting is at no cost to the applicant or nonapplicant.

13. Estimate of Other Total Cost Burden to Respondents and Recordkeepers

The collection of information would not result in a cost burden beyond the hours burden cited above.

14. Annualized Cost to the Federal Government

CVM currently has 11 FTEs allocated for post marketing surveillance activities. If each FTE equals approximately \$115,000, the total FTE burden to the Federal Government would be \$1,265,000. CVM currently contracts document processing, which costs \$100,000 for the post marketing surveillance activities. The total cost burden to the Federal Government would be \$1,365,000.

15. Explanation of Program Changes or Adjustments

FDA estimated that the proposed rule would require an additional 400 responses above the number required under the previous regulation from 200 businesses. The estimated increased total annual workload from the proposed rule was 200 hours, or approximately one hour per business. FDA's estimates of the annual reporting and recordkeeping burden in the proposed rule addressed only the increased burden resulting from the new provisions of the proposed regulation. The estimate did not include the workload resulting from previously existing provisions of the regulation. FDA has amended the estimated reporting and recordkeeping burden charts to reflect the total burden of the rule. Furthermore, FDA's estimates are for the number of hours required to complete each response and not the number of hours per year per NADA holder.

16. Plans for Tabulation and Publication and Project Time Schedule

Information is not to be published for statistical use.

