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Report to the Chairman, Human Resources and Intergovernmental Relations Subcommittee, Committee on Government Operations, House of Representatives

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FOOD SAFETY AND QUALITY

FDA Needs Stronger Controls Over the Approval Process for New Animal Drugs

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GAO

United States
General Accounting Office
Washington, D.C. 20548

Resources, Community, and
Economic Development Division

B-246269

January 17, 1992

The Honorable Ted Weiss
Chairman, Human Resources and Intergovernmental
Relations Subcommittee
Committee on Government Operations
House of Representatives

Dear Mr. Chairman:

In a pending case, the Food and Drug Administration (FDA) has accused a major drug company of manipulating data supporting a new animal drug. This case has raised concerns about the adequacy of FDA's ability to ensure the integrity of manufacturer-submitted data. Concerned about the possibility of FDA's approving new animal drugs on the basis of invalid data, you requested, on October 23, 1990, that we review FDA's efforts to ensure the accuracy and integrity of data provided by animal drug manufacturers (sponsors) as part of the approval process for new animal drugs.

About 80 percent of U.S. livestock and poultry are treated with animal drugs during their lifetime for therapeutic, reproductive, and production purposes. Because animal welfare and public health may be threatened by ineffective and/or harmful animal drugs, the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, requires that FDA determine whether new animal drugs for use in food-producing animals, such as antibiotics for use in dairy cows, are safe and effective for those animals and whether the edible products derived from treated animals, such as milk, will be safe for human consumption.

Under FFDCA, animal drug sponsors are responsible for demonstrating the safety and effectiveness of their products by submitting data to FDA as part of the approval process for new animal drugs. FDA relies on two internal controls to ensure the accuracy and integrity of sponsor-submitted data: (1) a scientific review of sponsor-submitted data and (2) the Bioresearch Monitoring Program, which verifies that animal drug data are prepared in compliance with federal guidelines and are substantiated by original records.

Results in Brief

FDA cannot ensure the integrity and accuracy of animal drug data because of weaknesses in its two main controls over data submitted by manufacturers to support the safety and efficacy of new animal drugs.

First, FDA's scientific review is designed to detect data of poor scientific quality or of questionable value. However, over 40 percent of FDA's data reviewers, while highly qualified, are new to the review process and lack adequate training to effectively assess data. Second, FDA primarily relies on its Bioresearch Monitoring Program to detect fraudulent data. But significant structural flaws in this program—such as a lack of adequate regulations, an insufficient number of inspections, untimely inspections, and weaknesses in the management information system—do not allow the program to effectively support the scientific data review.

The objective of the Bioresearch Monitoring Program is to inspect at least one study for each new animal drug approval. However, FDA did not conduct any inspections to verify the accuracy and integrity of data supporting 54 percent of the new drugs for food-producing animals that it approved from fiscal years 1985 through 1990. Consequently, over half of the new animal drugs that FDA approved during this period were approved solely on the basis of its scientific data review. Since this data review is not designed to be the primary mechanism for detecting fraudulent data, these new animal drugs may be supported by data of unknown validity.

Although FDA can improve its Bioresearch Monitoring Program, it may be unable to conduct a sufficient number of inspections because of competing priorities for inspection resources. FDA may need additional resources to maintain and/or expand its inspection activities. Funding alternatives are limited, but one source of additional funding could be user fees to cover the cost of approving new animal drugs, including the costs of conducting bioresearch monitoring inspections.

FDA's inadequate procedures to ensure the integrity of animal drug data make FDA vulnerable to the possibility of approving new animal drugs for food-producing animals on the basis of invalid, inaccurate, or fraudulent data. Under the Federal Managers' Financial Integrity Act, this deficiency constitutes a material internal control weakness because FDA may be unable to fulfill its mission to protect the health and safety of animals and people. Furthermore, the Department of Health and Human Services (HHS), FDA's parent organization, has not complied with the requirements of the Federal Managers' Financial Integrity Act because it has not fully assessed the internal controls for the approval of new animal drugs and, as a result, has not identified or reported any material weaknesses in this program to the President.

Background

Under FFDCA, FDA is responsible for ensuring that new animal drugs are safe and effective for their intended use and do not result in unsafe residues in foods from treated animals. Unsafe animal drug residues in food could result in potentially dangerous health consequences for consumers, such as allergic reactions and cancer. In addition, some scientists are concerned about the potential problem of increasing the prevalence of drug-resistant bacteria from the use of animal drugs. Therefore, most new animal drugs must receive approval from FDA before they can be legally marketed in the United States.

Drug sponsors must demonstrate that new animal drugs are safe and effective. To do this, drug sponsors submit a new animal drug application (NADA) to FDA, along with supporting studies and evidence from toxicology, pharmacology, and clinical trials.

FDA's Center for Veterinary Medicine (CVM) is responsible for reviewing NADAs. This review consists of two phases—the investigational new animal drug (INAD) phase and the NADA phase. During the investigational phase, drug sponsors conduct the necessary safety and effectiveness studies to support the claims of the new animal drug. During the NADA phase, scientists in the Office of New Animal Drug Evaluation review the application to assess the scientific validity and sufficiency of the supporting data. FDA scientists review at least 18 required safety and efficacy studies for each new drug application for food-producing animals. FDA approves an average of 17 new drugs for food-producing animals every year.

Generally, FDA does not conduct corroborative studies to validate sponsor-submitted data. Instead, to ensure the accuracy and integrity of these data, FDA relies on the Bioresearch Monitoring Program operated by its Office of Surveillance and Compliance. The objectives of this program are to (1) ensure that toxicology laboratories, drug sponsors, clinical investigators,[1] and study monitors[2] comply with FFDCA and FDA requirements and (2) assess, through audits, whether the original records substantiate the data submitted to FDA in support of the NADA. To meet its objectives, the Bioresearch Monitoring Program relies on FDA

[1]A clinical investigator is a person qualified by scientific training or experience to evaluate the safety and effectiveness of new animal drugs.

[2]A study monitor is a person appointed by the drug sponsor to monitor the clinical investigations being conducted to support the safety and efficacy of the new animal drug.

field offices to conduct surveillance or directed inspections[3] of drug sponsors, monitors, laboratories, and clinical investigators.

Data Review Is Not the Primary Mechanism for Detecting Fraudulent Data

CVM's scientific data review is designed to ensure that (1) the drug sponsor has submitted sufficient evidence to support the safety and efficacy labeling claims of the new animal drug and (2) the drug sponsor and study generators have exercised good scientific judgment in deciding on the safety and efficacy of the drug. According to CVM officials, data reviewers can detect data of poor scientific quality or of questionable value. For example, data reviewers identified one study in which the drug used in the clinical trial differed from the drug in the NADA, and another study in which the drug sponsor had assigned test animals systematically rather than randomly during a trial. However, the data review is not intended to be the primary mechanism to detect fraudulent data.

While data reviewers may be able to detect data of poor quality or questionable value, lack of experience may hamper their ability to do so. Although there are no formal FDA criteria, according to CVM officials, new reviewers generally require between 2 and 5 years of data review experience to learn FDA's regulatory process. CVM's new reviewers are highly qualified and have advanced degrees in veterinary medicine and animal science; however, they account for about 41 percent of CVM's total data review staff and have less than 2 years of regulatory experience. This has occurred because, between 1988 and 1991, a significant number of FDA reviewers retired or were reassigned. FDA hired new reviewers to cover these losses as well as to augment its staff because its allocated number of full-time employees had increased. For example, in the Division of Toxicology and Environmental Sciences, half of the data reviewers are new. This Division is a critical one that determines the safety of food products derived from animals treated with drugs. Moreover, between 1990 and 1991, the Division had not had a permanent director, but had five different acting directors.

Despite their inexperience, new reviewers do not receive formal training in reviewing studies and data supporting NADAs. Their training is generally related to administrative procedures. In lieu of formal reviewer training, CVM's division directors strongly emphasize on-the-job training,

[3]A directed inspection is conducted for a specific purpose, such as (1) prior knowledge or suspicion of violations, (2) the need to focus the inspection on a specific part of the study, or (3) the need to expand the inspection to cover multiple studies.

and branch chiefs within each division review the work performed by new reviewers.

We found a lack of consensus among CVM officials we talked to about the qualifications a reviewer needs to fulfill the objectives of the data review process and accurately assess the safety and efficacy of a new animal drug. The Director and other officials in the Office of New Animal Drug Evaluation believe that new data reviewers are sufficiently qualified and do not require additional training in the scientific review process to effectively review NADAs. However, during the course of our review, several division directors and branch chiefs we interviewed on an individual basis believed that formal training should be provided to data reviewers. Although new data reviewers may have the scientific knowledge to review studies, their lack of regulatory experience may limit their ability to apply that knowledge to FDA's regulatory process. Formal reviewer training could alleviate this concern and perhaps better ensure that applications for new animal drugs are effectively reviewed.

Some training courses on the scientific review process will be provided to new reviewers in the near future. In addition, because of the large number of data reviewers hired by CVM, the 1982 Reviewers Training Manual was updated during the course of our review and distributed to all new reviewers.

According to CVM officials, data reviewers may not be able to detect fraudulent data if the data are presented in a manner that appears to be scientifically valid. Therefore, reviewers must rely on the Bioresearch Monitoring Program to verify their concerns about and ensure the integrity of sponsor-submitted data.

Structural Flaws Make the Bioresearch Monitoring Program Ineffective

CVM data reviewers depend on the Bioresearch Monitoring Program to conduct inspections to verify the integrity of sponsor-submitted data supporting new animal drugs. However, data reviewers cannot rely on the Bioresearch Monitoring Program to ensure the integrity and validity of sponsor-submitted data because of (1) a lack of adequate regulations, (2) an insufficient number of inspections, (3) untimely inspections, and (4) a weak management information system.

CVM is considering a number of initiatives to improve the effectiveness of the Bioresearch Monitoring Program. Because these initiatives are in

various stages of development, we cannot determine whether they will ultimately address our concerns.

Lack of Adequate Regulations

The Bioresearch Monitoring Program includes three compliance programs to help ensure that studies are conducted according to good laboratory and clinical investigation practices.

- The Good Laboratory Practice Program requires FDA to inspect, every 2 years, toxicology laboratories that perform safety studies to support drug approvals, to ensure that these laboratories comply with the good laboratory practice regulations.
- The Clinical Investigator Program requires clinical investigators to observe FDA guidelines when performing clinical investigations with new animal drugs.
- The Sponsor/Monitor Program requires drug sponsors and study monitors to monitor under FDA guidelines all clinical investigations being conducted with the new animal drug.

FDA's ability to enforce compliance with the Clinical Investigator and Sponsor/Monitor Programs may be limited because neither program is adequately covered by regulations. According to FDA officials, both programs are included in FDA's regulations for new animal drugs for investigational use. We found that the existing regulations provide a limited description of some of the responsibilities of drug sponsors, such as the need to monitor clinical trials and to ensure the qualifications of clinical investigators. However, the regulations do not detail responsibilities of either drug monitors or clinical investigators. According to an FDA field inspector, because drug manufacturers know that these two programs are based largely on FDA guidelines, citations for compliance violations have little impact.

In contrast, FDA headquarters officials told us that the promulgation of the good laboratory practice regulations in 1979 improved the quality of the data developed by toxicology laboratories to support the safety claims of new animal drugs. These officials believe that similar regulations are needed for the Sponsor/Monitor and Clinical Investigator Programs to ensure that data of good quality are collected during clinical investigations and to provide FDA with stronger enforcement capabilities.

FDA proposed regulations in 1977 and 1978, respectively, for the Sponsor/Monitor and Clinical Investigator Programs. According to CVM

officials, these regulations were never made final because of the overall deregulation environment at that time. However, we found that FDA has specified detailed drug sponsor and clinical investigator responsibilities in its regulations for human drugs. Furthermore, according to the Coordinator of the Bioresearch Monitoring Program for all drug approvals, animal and human, the lack of adequate regulations to monitor and conduct clinical investigations for animal drugs has made CVM's compliance programs the weakest in FDA.

Insufficient Number of Inspections

FDA has approved many new animal drugs without a single inspection to ensure the integrity of sponsor-submitted data, including safety data developed in foreign countries. FDA policy requires data reviewers to identify critical safety and efficacy studies (also called pivotal studies) for each drug approval as early in the review process as possible and to request inspections through the Bioresearch Monitoring Program. However, FDA has no criteria on the number of studies that should be inspected for each approval. Although the Reviewers Training Manual states that the objective of the Bioresearch Monitoring Program is to ensure that at least one pivotal study for each new animal drug is inspected, the program had not inspected any pivotal study for 43, or about 54 percent, of 79 new drugs approved for food-producing animals from fiscal years 1985 through 1990.[4]

FDA allows drug sponsors to use data developed in foreign countries to support the safety of new animal drugs if the data meet the FDA regulations and guidelines applicable to domestic data. Foreign safety studies accounted for at least 60 percent of all safety data cited in those NADAs that had foreign data. However, only 6 of the 30 foreign laboratories that conducted these studies were inspected for compliance with the good laboratory practice regulations. For the majority of foreign safety studies, FDA relied solely on the assurance of drug sponsors that the foreign laboratories had complied with FDA requirements.

According to FDA officials, the Bioresearch Monitoring Program cannot conduct an adequate number of inspections because of competing field inspection priorities, a backlog of inspection requests, poor coordination between the Office of New Animal Drug Evaluation and the Office of

[4]FDA also approved 24 other new animal drugs for food-producing animals during this time for which no new data were required. However, we were unable to determine the inspection status of the studies supporting these drugs because of limitations in CVM's management information system, which is discussed below.

Surveillance and Compliance, and limited inspection resources. In September 1990, to reduce the inspection backlog, FDA canceled all outstanding low-priority inspections assigned to the field and issued only requests for high-priority directed inspections to the field for the following year.

However, FDA's field resources are still inadequate to satisfy these requests. For example, during fiscal year 1991, 116 directed inspection requests from the Office of New Animal Drug Evaluation were assigned to the field. However, FDA's field staff were able to complete only 20 of the 116 requests by September 1991. The outstanding 96 requests were carried over into fiscal year 1992.

Untimely Inspections

Because FDA inspections are often conducted on already completed studies, it is more difficult to detect fraudulent and manipulated data, according to some FDA field inspectors. Such detection is difficult because (1) study animals are no longer available for examination and (2) data have already been generated, but their origins and development are unknown. For example, when examining a completed study, an inspector may not be able to detect whether animals were switched or an extra drug was used during the study.

Also, if studies are inspected after a significant lapse of time, complete and original records may not be available for review. For example, an FDA field inspector found original records of a clinical trial during an inspection that differed significantly from the records made available for inspection by the clinical investigator. The original records were with the person who had conducted the trial, but this person was told by the clinical investigator to destroy the records in his possession when he left the job.

FDA headquarters officials concur that inspections of ongoing studies are probably the most effective way of ensuring the validity and integrity of new animal drug data. Currently, FDA requires drug sponsors to submit a "Notice of Claimed Investigational Exemption for a New Animal Drug" prior to shipment of the drug to clinical investigators, but the regulations do not specify how far in advance of shipment FDA must receive this notice. Consequently, there may not be enough time under the current system to schedule inspections during clinical trials. In the future, according to a division director, FDA may require 6 weeks advance notification by drug sponsors. This requirement has been included in CVM's current draft of the regulations for investigational new animal drugs.

However, even if FDA implements this requirement, the low priority for bioresearch monitoring inspections and limited field resources may continue to delay inspections until after a study has been completed.

Weak Management Information System

CVM's management information system cannot provide data reviewers and FDA management with reliable and adequate inspection data to assist in reviewing NADAs or in efficiently allocating limited inspection resources. Before a NADA can be approved, data reviewers must obtain a history of all FDA inspections of the sponsor/monitors, laboratories, and clinical investigators associated with the new animal drug. This history enables data reviewers to determine if there have been any past compliance violations. However, CVM has no user documentation explaining how to enter data into the data base for the Bioresearch Monitoring Program. As a result, information in the data base is inconsistent and nonuniform. This lack of formal policies and procedures indicates that FDA has inadequate controls in place to ensure the reliability of the information generated by this data base. Consequently, data reviewers are using inspection data that may be incomplete during their review of NADAS.

Furthermore, CVM's management information system cannot provide basic inspection information for new animal drug approvals, such as how many inspections were performed and which studies were inspected. FDA assigns a four-digit INAD number to each new animal drug during the investigational phase and a six-digit NADA number when an application is submitted to FDA for final drug approval. Because many FDA inspections are performed during the investigational phase, a data reviewer needs to know what inspections have been conducted under both the drug's INAD number and NADA number. CVM's management information system is unable to make this link, and CVM has been relying on data reviewers for this information, many of whom, as noted above, are new reviewers. As a result, data reviewers are not always able to make a complete NADA and INAD link. For example, we asked FDA to link 103 NADA numbers, for drugs approved from fiscal year 1985 through 1990, to their corresponding INAD numbers. FDA data reviewers were able to provide us with INAD information on 73 of the 103 NADAS and told us that obtaining the other 30 links would require a time-consuming manual search through the original NADA files.

CVM's management information system also cannot provide FDA officials with the data needed to help them decide how best to allocate and

manage limited inspection resources. CVM's system cannot identify critical or high-volume sponsor/monitors, laboratories, or clinical investigators that should be targeted for inspection. This situation compounds the problem of limited resources for conducting inspections. For example, when we manually matched CVM's inspection data with Freedom of Information summaries of new animal drug approvals, we found that FDA had not inspected about 42 percent of the clinical investigators who had performed efficacy studies for four or more different new animal drugs approved from fiscal years 1985 through 1990.

FDA May Need More Funding for Inspections

The inability of the Bioresearch Monitoring Program to conduct an adequate number of inspections of ongoing studies is largely due to limited inspection resources and competing priorities for these resources, according to FDA officials. FDA has identified the collection of user fees as a possible solution to its problem of limited resources. HHS' Office of Inspector General, in July 1990, also identified the collection of user fees as a possible solution to FDA's problem of limited resources. The Inspector General's report stated that the regulated industry should contribute to the cost of ensuring the safety and effectiveness of its products because the industry receives benefits from FDA's regulatory activities in the form of increased consumer confidence and protection from liability.

The Advisory Committee on the Food and Drug Administration[5] also acknowledged FDA's resource problems in its May 1991 report. While the Committee did not take a position on any specific proposal for augmenting FDA's funding, it recommended considering alternative sources of funding for FDA, including user fees. The report also stated that any alternative source of funding for FDA should (1) supplement—not substitute—an adequate base of appropriations for the agency and (2) be tied to specific improvements in the agency's functions.

Currently, FDA imposes user fees for certifying color additives, supervising the destruction and reconditioning of products, and inspecting imported tea, among other things. These user fee programs are the result of specific legislation authorizing FDA to collect such fees. During the last several years, FDA has requested expanded user fee authority from the Congress for activities such as the pre-market approval of

[5]Final Report of the Advisory Committee on the Food and Drug Administration (Washington, D.C., May 1991). The Committee is commonly known as the Edward's Committee, after Charles C. Edwards, M.D., Chairman.

products. However, the Congress has prohibited the agency from collecting new user fees that are not specifically authorized by inserting specific language in its annual appropriation acts. In effect, the Congress has told FDA that it must seek, on a case-by-case basis, authority to charge user fees.

FDA's Internal Control Program for CVM Is Materially Deficient

FDA has not complied with the requirements of the Federal Managers' Financial Integrity Act (FMFIA) for program internal controls, including CVM's pre-market approval program for new animal drugs. Under the act, FDA, as part of HHS, is required to establish and maintain a system of internal controls to provide reasonable assurance that, among other things, program and administrative activities are effectively managed to achieve the goals of the agency. As defined by FMFIA, a material weakness exists in an agency's internal control systems when the agency lacks reasonable assurance that the objectives of the system are being accomplished and when the weaknesses could significantly impair the fulfillment of the agency's mission and/or deprive the public of a needed service.

Because neither FDA's scientific data review nor Bioresearch Monitoring Program is adequately ensuring the integrity of the data supporting new animal drugs, FDA is approving drugs on the basis of data of unknown validity. This is a material internal control weakness because public health and animal welfare may be endangered if FDA approves new animal drugs for food-producing animals on the basis of invalid, inaccurate, or fraudulent data.

In addition, HHS has not complied with the internal control evaluation and reporting requirements of the act as they pertain to FDA. Under FMFIA, an agency must evaluate its internal controls annually and report to the President on whether these controls comply with the objectives established by the act and the standards prescribed by the Comptroller General and, if they do not, describe a plan for corrective action. FDA did not complete its first required Management Control Plan[6] until April 1991 and its risk assessment for the pre-market approval program for animal drugs until December 1991, nearly 4 years after the December 31, 1987, deadline. FDA's Management Control Plan identified the pre-approval program for animal drugs as one of CVM's three critical program components; however, FDA's risk assessment for the program did

[6]A Management Control Plan identifies the agency's program components and the risk rating of each component, and provides a plan for necessary internal control evaluations over a 5-year period.

not assess the vulnerability of the program to fraudulent data. In addition, the act requires agencies to evaluate whether their internal control systems are in compliance. The first internal control evaluation of CVM's pre-approval program for animal drugs and food additives will not be completed until April 1992, according to agency officials.

Conclusions

Without adequate controls to verify the accuracy and integrity of new animal drug data, FDA cannot fully meet its mission of ensuring the safety and effectiveness of new animal drugs and the safety of food derived from treated animals. FDA's new data reviewers, although highly qualified, are not provided with adequate training on the regulatory review process to facilitate their review of applications. Furthermore, FDA relies on the Bioresearch Monitoring Program to ensure the integrity of sponsor-submitted data. However, weaknesses in this program make it an ineffective internal control. The program lacks adequate regulations, does not conduct a sufficient number of inspections, conducts untimely inspections, and has a weak management information system. Therefore, FDA has been relying solely on the scientific data review, which is not designed to detect fraudulent data, for approving about 50 percent of the new animal drugs for food-producing animals. An improved Bioresearch Monitoring Program, especially an improved management information system, would allow FDA to more effectively target its existing inspection resources to ensure the safety and efficacy of new animal drugs.

These improvements alone may not be sufficient to ensure the integrity of sponsor-submitted data. Because of competing, high-priority demands for FDA's inspection resources, FDA may need additional resources to maintain, even more to expand, its bioresearch monitoring inspections. To maintain and/or expand its inspections, FDA may need to seek additional funding or specific authority to charge and retain user fees for approving new animal drugs, including the costs of conducting bioresearch monitoring inspections—an integral part of the approval process. The sufficiency of FDA's existing level of funding for bioresearch monitoring inspections of data supporting new animal drug applications raises a larger policy issue of whether the approval process for new animal drugs should be supported by earmarked user fees. In light of existing constraints on federal resources and the importance of regulating the safety and efficacy of animal drugs, providing FDA with specific authority to charge user fees for approving new animal drugs may be a viable alternative to appropriations for funding this program.

Although we recognize that FDA cannot completely ensure the integrity of all sponsor-submitted data, we believe that FDA's lack of sufficient controls is a material internal control weakness. This weakness should be, but has not been, reported to the President as required by FMFIA, as part of HHS' annual report.

Recommendations

To improve FDA's controls over the accuracy and integrity of new animal drug data, we recommend that the Commissioner, FDA, direct the Director, CVM, to

- follow through with CVM's plans to provide training and guidance to new data reviewers on the scientific review of new animal drug applications;
- propose regulations detailing the responsibilities of sponsor/monitors and clinical investigators;
- establish criteria for the number of pivotal studies that should be inspected as part of the new animal drug approval process;
- require drug sponsors to provide adequate advance notification before shipping drugs for clinical trials in order to allow FDA to conduct inspections while trials are ongoing;
- improve CVM's management information system by developing (1) a system that can track all inspections and sponsor-submitted studies performed throughout the drug approval process and (2) system standards, procedures, and documentation for ensuring uniform, accurate, and complete data in the bioresearch monitoring data base; and
- use CVM's improved management information system to identify critical inspection needs and direct limited inspection resources to these needs.

If after taking these actions FDA can document that it needs additional resources to expand its inspection activities for approving new animal drugs, we recommend that the Secretary of Health and Human Services consider asking the Congress for additional funding or specific authority to charge user fees earmarked to pay for the expenses of approving new animal drugs, including the costs of conducting bioresearch monitoring inspections.

We also recommend that the Secretary of Health and Human Services include FDA's lack of sufficient controls to ensure the accuracy and integrity of sponsor-submitted animal drug data as a material weakness in his next internal control report to the President, as required by FMFIA.

Matter for Congressional Consideration

The Congress should consider the larger policy issue of whether the existing approval process for new animal drugs should be supported by user fees, regardless of the need to expand the number of bioresearch monitoring inspections. Furthermore, if the Congress authorizes user fees for approving new animal drugs, it should consider earmarking these funds for FDA to conduct this program.

Our work was conducted from November 1990 to September 1991 at FDA headquarters in Gaithersburg and Rockville, Maryland, in accordance with generally accepted government auditing standards. (Further details on our objectives, scope, and methodology are provided in app. I.)

We discussed the information in this report with officials in FDA's CVM and made changes where appropriate. The officials generally disagreed with our conclusion that FDA is unable to adequately ensure the integrity of sponsor-submitted data. However, they did agree with our recommendations to the agency. As requested by your office, we did not obtain written agency comments on a draft of this report.

As arranged with your office, unless you publicly announce its contents earlier, we will make no further distribution of this report until 30 days after the date of this letter. At that time we will send copies to the Secretary, HHS; the Commissioner, FDA; and interested congressional committees. We will also make copies available upon request.

This review was conducted under the direction of John W. Harman, Director, Food and Agriculture Issues, who may be reached at (202) 275-5138 if you have any questions. Other major contributors to this report are listed in appendix II.

Sincerely yours,

J. Dexter Peach
Assistant Comptroller General

Objectives, Scope, and Methodology

In an October 23, 1990, letter, the Chairman, Human Resources and Intergovernmental Relations Subcommittee, House Committee on Government Operations, requested that we review the adequacy of the Food and Drug Administration's (FDA) efforts to ensure the accuracy and integrity of data provided by drug manufacturers as part of the approval process for new animal drugs.

To obtain information on FDA's efforts to ensure the integrity of data, we interviewed officials and obtained documents from the Center for Veterinary Medicine (CVM) and the Office of Regulatory Affairs, at FDA's headquarters in Gaithersburg and Rockville, Maryland. To obtain information on the effectiveness of FDA's controls to detect fraudulent and manipulated data, we interviewed the directors of all four divisions and the Chief of the Quality Control Staff of the Office of New Animal Drug Evaluation. We also contacted six FDA district offices responsible for conducting the majority of CVM's bioresearch monitoring inspections—Atlanta, Georgia; Dallas, Texas; Denver, Colorado; Kansas City, Kansas; Los Angeles, California; and Newark, New Jersey. In addition, we contacted FDA's Office of Management and Operations to obtain information on FDA's compliance with the Federal Managers' Financial Integrity Act for internal control programs.

To obtain information on the number of supporting studies conducted and the names and number of laboratories, drug sponsors, and clinical investigators conducting the studies for new animal drugs approved for food-producing animals between fiscal years 1985 and 1990, we reviewed the Freedom of Information summaries available to the public for 103 new animal drugs.[1] To determine the effectiveness of FDA's inspection program, we used information only for those new animal drugs that cited new data in their Freedom of Information summaries. Of the 103 summaries, only 79 had some new data, and 24 referenced other approved new animal drugs or existing data. We also reviewed the original new animal drug application records at FDA's Document Control Unit to obtain the corresponding investigational new animal drug numbers for 30 new animal drug applications that FDA could not link for us.

To assess the adequacy of FDA's inspection activities to ensure the integrity of new animal drug data, we used data from CVM's Bioresearch Monitoring Program data base from March 1977 through May 1991. This

[1]Although 104 new animal drugs were approved during the 6 fiscal years that we reviewed, one Freedom of Information Summary was not available, and therefore we could not include it in our review.

data base contains information on all bioresearch monitoring compliance inspections performed by FDA field inspectors on drug sponsors/monitors, clinical investigators, and laboratories. We discussed the policy and procedures used to maintain the data base with Bioresearch Monitoring Program officials. CVM's Bioresearch Monitoring Program staff told us that they had verified the completeness of the data base by comparing it with the information maintained in their card files and file folders. However, we did not independently verify the reliability of the data base because of resource and time constraints. Although the Bioresearch Monitoring data base has some limitations, it has the only official data available, and we believe that when these data are viewed in context with other available evidence, the conclusions and recommendations in this report are valid.

Our work was conducted from November 1990 to September 1991 in accordance with generally accepted government auditing standards.

We discussed the information in this report with officials at FDA's Center for Veterinary Medicine. Where appropriate, changes have been made on the basis of these discussions to further clarify the information presented. Although agency officials disagreed with our conclusion that FDA could not adequately ensure the integrity of sponsor-submitted data, they agreed with our recommendations. As requested by your office, we did not obtain written agency comments on a draft of this report.

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