

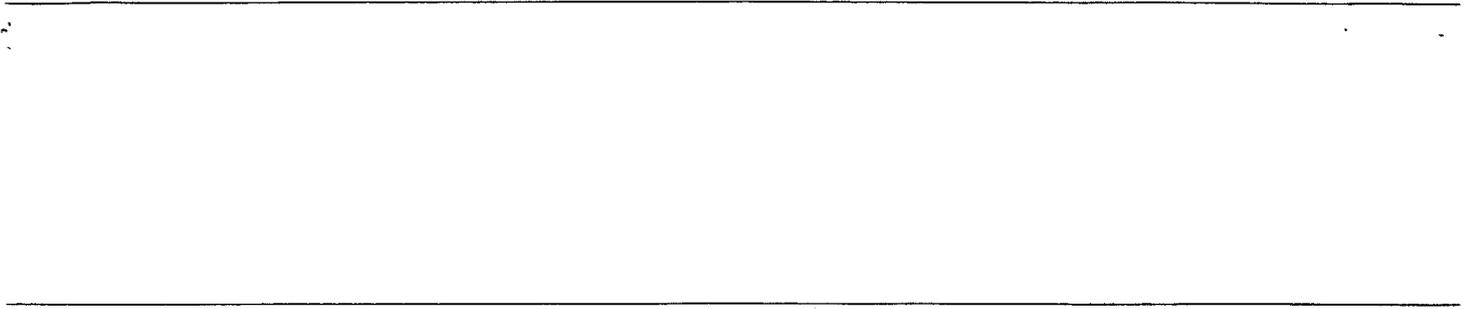
September 1988

# FDA'S REVIEWS OF NEW DRUGS

## Changes Needed in Process for Reviewing and Reporting on Clinical Studies



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

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Human Resources Division

B-224063

September 12, 1988

The Honorable John Heinz  
Ranking Minority Member  
Special Committee on Aging  
United States Senate

Dear Senator Heinz:

This report responds to your November 4, 1986, request that we review activities of the Division of Scientific Investigations in the Food and Drug Administration (FDA). In the report, we focus on the need for coordinating and achieving more timely reviews of clinical studies submitted to FDA in support of new drug applications. The report recommends steps that FDA can take to improve its coordination and performance of the reviews.

Unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of this letter. At that time, we will send copies to the Secretary of Health and Human Services, the Commissioner of FDA, the Director of the Office of Management and Budget, and other congressional committees and interested parties. We also will make copies available to others on request.

Sincerely yours,

*for* Edward A. Blensmore  
Lawrence H. Thompson  
Assistant Comptroller General

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# Executive Summary

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## Purpose

Assuring American consumers that new drugs and biologics entering the marketplace are safe and effective is a responsibility of the Food and Drug Administration (FDA). Through inspections and reviews, FDA's Division of Scientific Investigations attempts to verify the integrity of scientific testing and the reliability of test data submitted to FDA in support of new drug applications.

In November 1986, the Chairman (now the ranking minority member) of the Senate Special Committee on Aging asked GAO to review the Division's activities, including its responsibilities relating to the approval of new drug and biologic products; the accuracy of FDA data and adequacy of oversight regarding clinical investigators, institutional review boards, and toxicology laboratories involved in studies supporting new drug applications; FDA's review of studies by clinical investigators supporting new drug applications; the adequacy and timeliness of "for-cause" (specially requested) inspections; and enforcement actions resulting from the Division's work. GAO also examined the timeliness of the Division's inspections.

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## Background

Between fiscal years 1977 and 1987, FDA's Division of Scientific Investigations conducted or directed more than 5,400 inspections and reviews including the work of over 2,200 clinical investigators, almost 2,400 institutional review boards, and over 500 toxicology laboratories. District office field staff perform most inspections, using guidance from FDA headquarters. GAO's examination of the Division's work was done before a late 1987 reorganization that affected some of its responsibilities.

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## Results in Brief

FDA's computerized listings of the review boards and toxicology laboratories involved in studies supporting new drug applications are adequate for scheduling inspections of these entities. It has had problems maintaining accurate information on clinical investigators, but has moved to improve this.

For each new drug application submitted to FDA, the general policy of the Division of Scientific Investigations is to review at least two important clinical studies supporting it. The number actually reviewed varies, however. But generally, there was no evidence that the FDA officials who determined new drug safety and efficacy considered the results of these reviews and the Division's recommendations, as FDA policy requires. Better communication and coordination among FDA units would help ensure that they have such information.

With respect to for-cause inspections of clinical investigators and sponsor/monitors, Division staff often participated. But their participation had little effect on the severity of violations found. For-cause inspections performed in fiscal years 1982-86 were timely, most done within 6 months of being assigned.

The reviews of clinical studies supporting new drug applications often lagged. Of 190 reviews scheduled for 41 new drugs GAO examined, less than half were done within 12 months after the application was submitted. At the time of GAO's review, FDA had established no timeframes for such reviews, even though in May 1987 it set a goal of reducing to 12 months the time required to review and act on new drug applications.

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## Principal Findings

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### Information on Review Boards, Laboratories, Investigators Adequate

GAO found no reason to believe that FDA's database of information on review boards and laboratories was not sufficiently accurate and complete for use in scheduling inspections. (See p. 14.) FDA has had problems maintaining accurate information on investigators, but has moved to improve this. As of July 1986, FDA had a 9-month backlog of data awaiting entry into its computerized inventory of clinical investigators. But since then, it has increased the number of staff who maintain the database and changed regulations to make it easier for staff to identify clinical investigators. Consequently, the backlog has been eliminated and the database is more reliable, FDA officials said.

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### Review of New Drug Studies: Better Coordination Needed

Improved communication and interaction between the Division of Scientific Investigations and FDA's drug review divisions would provide greater assurance that the most important drug studies are reviewed and that officials who review new drug applications are aware of the results of the Division's reviews. FDA's policy manual, which gives the drug review divisions responsibility for selecting studies for review, is being revised to assign joint responsibility for this task to the drug review divisions and the Division of Scientific Investigations. In two drug review divisions, GAO found that medical officers reviewing new drug applications did not select the specific studies to be reviewed nor coordinate with the Division in the selection. In only 27 of 190 instances examined by GAO were review results documented in the files accompanying the applications. (See pp. 16-17.)

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### Division Participation Has Little Effect on Results of For-Cause Inspections

Over the past 10 years, the Division of Scientific Investigation has assigned or conducted over 400 for-cause inspections of clinical investigators and sponsor/monitors. Usually, these are done because the clinical study involved is of particular importance to a new drug application, some wrongdoing is indicated, or the investigator is conducting an unusually large number of studies. Of 181 such inspections during fiscal years 1982-86, Division staff directly participated along with district investigators in 124 (69 percent). "Official action" was initiated in 16 percent of the 124 investigations, voluntary action in 64 percent, and no action in 20 percent. These results are quite similar to results for the 57 inspections in which the Division did not participate. Thus, judging from the severity of findings, lack of participation by the Division had little effect on the inspection results. However, participation by Division staff should be encouraged so that the staff can maintain their knowledge about particular drugs and better interact with the drug review divisions. (See pp. 24-26.)

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### Timeliness of Inspections: Coordination Within FDA Often a Factor

FDA scheduled 190 reviews of studies supporting the 41 new drug applications GAO examined. Fewer than half of these (88) were completed within 12 months of FDA's receipt of the application. For nearly three-quarters (73) of the remainder, FDA did not notify its district offices of the need to make reviews until at least 1 year after it received the application. Coordination problems within FDA contributed to increasing the time required to make review assignments to district offices. Once assigned, however, the reviews were completed in a timely manner. (See pp. 19-20.)

But Division officials told GAO that some district offices were having problems completing their fiscal year 1986 assignments. Because the cases GAO first examined had been assigned earlier and were done in a timely manner, GAO selected a second sample. The sample covered clinical investigator reviews assigned in fiscal year 1986. This was the most recent year for which information was available. Of 240 reviews completed by the time of the GAO review, 24 percent were done within 3 months and 70 percent within 6 months of the date assigned. The remaining 30 percent took from 7 months to over 1 year. District involvement in other high priority work, such as investigating product-tampering incidents, was cited as one reason for delay in completing the less timely assignments. (See pp. 20-21.)

Inspectors' time could be cut in half and a significant amount of clerical support time saved on inspection reports, district office officials told

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GAO. Because some long inspection reports contain few if any adverse findings, they explained, it would be more efficient to allow abbreviated reports to be made where there was substantial compliance with FDA requirements. (See p. 21.)

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## Recommendations

GAO is making several recommendations to the Secretary of HHS to improve the scheduling process for inspections and thus help FDA meet its goals for processing new drug applications in a timely fashion. These include (1) changing the present quarterly assignment system to allow sending clinical investigator inspection assignments to district offices in a more timely manner, (2) requiring that FDA include a statement of the results of inspections by the Division of Scientific Investigations, with all new drug application packages being reviewed, and (3) allowing district offices to write abbreviated inspection reports when inspections are in substantial compliance with FDA requirements. (See pp. 22-23.)

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## Agency Comments

HHS concurred with all of GAO's recommendations and pointed out actions it was taking in response to the recommendations. These actions include (1) revising the system for sending inspection assignments to district offices so that they are sent out sooner, (2) requiring a statement in new drug approval decision packages on the results of the Division's inspections, and (3) allowing the use of abbreviated inspection reports when few or no deficiencies are noted. (See pp. 30-33.)

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**Abbreviations**

DSI	Division of Scientific Investigations
FDA	Food and Drug Administration
GAO	General Accounting Office
HHS	Department of Health and Human Services
NDA	new drug application

# Introduction

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In evaluating the safety and effectiveness of new drugs and biologics, the Food and Drug Administration (FDA) relies on data obtained by clinical investigators who conduct studies on humans. The premature marketing of a number of inadequately tested drugs was one factor that led to the passage of the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act in 1962 and to FDA's promulgation of Investigational Drug Regulations in 1963. These amendments and regulations required FDA to exercise greater control over clinical studies involving human test subjects to assure their greater protection as well as the integrity and reliability of the studies.

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## Background

FDA's Division of Scientific Investigations (DSI) (initially known as the Scientific Investigations Staff) was formed in 1967. Its primary function was to investigate the work of clinical investigators suspected of performing improper research. In 1985, DSI also assumed responsibility for monitoring studies related to biologics.<sup>1</sup>

DSI was located in FDA's Center for Drugs and Biologics until late 1987, when the Center became two separate organizations—the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. Each new organization has its own Office of Compliance, which has assumed responsibility for the bioresearch monitoring activities relating to its respective products. DSI became a division in the Center for Drug Evaluation and Research's Office of Compliance. DSI responsibilities relating to biologics along with one staff person were transferred to the Center for Biologics Evaluation and Research's Office of Compliance.

In carrying out its monitoring efforts, DSI is responsible for maintaining close working relationships with FDA's six drug review divisions<sup>2</sup> and conducts or directs inspections of clinical investigators, institutional review boards, toxicology (nonclinical) laboratories, sponsor/monitors, and radioactive drug research committees. The purpose of these inspections is to assure the integrity of the scientific testing process, the reliability of test data submitted to FDA, and the protection of human test subjects.

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<sup>1</sup>A biological product is defined in the Public Health Service Act as any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man.

<sup>2</sup>During the period covered by this review, FDA had six drug review divisions. A seventh division was established in June 1987, and an eighth was established as part of the late 1987 reorganization.

DSI estimates that it is responsible for monitoring the activities of as many as 50,000 individuals and organizations involved in studies supporting new drugs and (before 1988) biologics, as follows:

- Clinical investigators, usually physicians who conduct the clinical studies of new drugs and biologics, administer the test products to patients, and report the results;
- Institutional review boards, made up of both medical professionals and citizens from the community and formally designated by an institution to approve the initiation of, and conduct periodic reviews of, biomedical research involving humans, paying particular attention to the protection of human subjects;
- Toxicology laboratories, which perform preclinical (animal) studies;
- Sponsor/monitors, generally drug firms that provide funding for the testing and monitoring of clinical studies performed by investigators; and
- Radioactive drug research committees, associated with medical institutions or with a committee established by a state to provide advice on radiation health matters and responsible for reviewing and approving the use of radioactive drugs for research involving human subjects.

Inspections conducted or directed by DSI are of two kinds:

- Those routinely assigned on a quarterly basis to FDA's district offices because a new drug application (NDA) has been submitted to FDA for approval. Over 80 percent of inspections of clinical investigators are routine and performed mostly without direct DSI participation.
- For-cause inspections, which involve greater participation by DSI staff, and generally are performed because (1) the drug review division questions the clinical investigator's data, (2) the clinical study is singularly important in the approval of a product, (3) there is some reason to suspect that the clinical investigator is not doing legitimate studies, or (4) a clinical investigator is conducting an unusually large number of studies, which may indicate insufficient attention being given to each study.

Under the direction of the Office of Regulatory Affairs, FDA's 21 district offices are responsible for performing bioresearch inspections for drugs and biologics according to standardized compliance guidance provided by FDA headquarters. Both for-cause and routine inspections are conducted by district office investigators specially trained to do so. DSI staff, who serve in a scientific advisory capacity to the district office investigators, often participate in for-cause inspections because of their subject matter knowledge about the specific drugs.

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Between fiscal years 1977 and 1987, DSI conducted or directed over 5,400 inspections of clinical investigators, institutional review boards, toxicology laboratories, sponsor/monitors, and radioactive drug review committees (see app. I). Since fiscal year 1980, DSI has averaged 573 inspections annually.

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## Objectives, Scope, and Methodology

In a 1986 fact sheet<sup>3</sup> developed for the Chairman of the Senate Special Committee on Aging, we pointed out that, although DSI's responsibilities had increased, (1) DSI staff devoted to bioresearch monitoring activities had been reduced from 37 to 30 since fiscal year 1981 and (2) DSI's travel funds had been reduced by 28 percent between fiscal years 1983 and 1986, resulting in a 25-percent decline in the number of inspections in which the staff were directly involved. In view of FDA's resource reductions for DSI, the Chairman (now ranking minority member) expressed concern about DSI's ability to carry out its regulatory responsibilities. In a letter of November 4, 1986, he asked that we review DSI's activities with particular emphasis on determining the following:

1. What the roles and responsibilities of DSI and FDA district offices are in the premarket regulation of drug and biologic products;
2. Whether DSI has accurate and complete information on active clinical investigators, institutional review boards, and toxicology laboratories and whether its oversight over these entities is adequate;
3. What FDA's policy is on review of important studies submitted by drug and biologics firms in support of applications for product approval;
4. Whether all important studies supporting drugs and biologics approved in the past 2 years were reviewed by DSI prior to product approval;
5. Whether FDA's for-cause inspections are adequate and timely; and
6. What enforcement actions FDA has initiated as a result of DSI inspections in each year since DSI was established.

To accomplish our objectives, we did the following:

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<sup>3</sup>Food and Drug Administration: Resources for Division of Scientific Investigations Have Been Reduced (GAO/HRD-86-136FS, Aug. 28, 1986).

- Reviewed regulations and guidelines governing the bioresearch monitoring program and the drug and biologics' approval process.
- Interviewed officials in (1) the Center for Drugs and Biologics' Office of Compliance, including DSI, (2) the drug and biologics review divisions, and (3) FDA's district offices in Baltimore, Dallas, and Los Angeles.
- Reviewed correspondence and other records related to the inventories of active clinical investigators, institutional review boards, and toxicology laboratories. We interviewed officials responsible for compiling and maintaining the inventories, and reviewed measures taken to improve their completeness and accuracy.
- Determined FDA policy for reviewing important studies, and selected and reviewed a sample of new drug and biologics applications approved during fiscal years 1985 and 1986 to determine whether DSI reviewed the important studies supporting product approval.
- Reviewed all bioresearch inspections for drugs and biologics assigned to FDA's district offices in fiscal year 1986 to determine the time required to complete these assignments.
- Reviewed and analyzed the results of for-cause inspections completed in fiscal years 1982-86. The requester was concerned about the adequacy of such inspections because on-site DSI staff participation in them had been reduced. We sought to determine (1) whether direct headquarters staff participation resulted in more serious violations being identified than when there was no such participation and (2) whether the inspections were completed in a timely manner. We did not review the fiscal year 1987 inspections, because the results of many would not have been finalized when we were performing our work. Nor did we attempt to determine the technical adequacy of individual inspections, as we lack the scientific expertise to do so. Information was not available to determine the relative contributions of the DSI staff person and the district investigator on inspections in which DSI staff participated.
- Obtained and reviewed information concerning enforcement actions initiated by FDA.

Of 202 drugs and biologics FDA approved in fiscal years 1985 and 1986, 68 were subject to DSI review, and of those, we selected a sample of 36 for our review. The other 134 were previously marketed drugs being reviewed, for example, for new uses or indications; drugs for which there were no clinical studies; or drugs such as isotopes and insulin not normally reviewed by DSI because it does not consider them important drugs. We focused our examination on drugs (1) where DSI had inspected two or fewer studies (according to FDA) and (2) that provided a cross section of work performed in FDA's drug review divisions. We also reviewed 5 drugs from the 134 that normally would not be reviewed by

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DSI to verify that the DSI decision not to review clinical studies was appropriate. Finally, we selected 6 of the 15 biologics licensed by FDA in fiscal years 1985 and 1986.

This report covers DSI activities prior to its reorganization in late 1987, at which time it no longer had responsibility for biologics. Our work, conducted between November 1986 and September 1987, with additional information obtained through April 1988, was done in accordance with generally accepted government auditing standards.

# Changes Needed in Coordinating and Achieving More Timely Reviews

DSI needs to improve its timeliness in scheduling and completing reviews of clinical investigators' studies and the communication and interaction between DSI and the drug review divisions. Less than half of the scheduled inspections on the 41 drugs in our sample were completed within a year of the date the new drug application was submitted to FDA. While FDA established a goal in May 1987 of reducing to 12 months the time for acting on NDAs, it has not established goals or time frames for completing inspections prior to the approval of an NDA. FDA medical officers in the drug review divisions were not always aware of DSI's findings, and the inspection results were not required to be included in the package of material submitted to the officials responsible for approving new drugs.

## Procedures for Selecting Inspectees and Studies for Review

Institutional review boards, toxicology laboratories, and radioactive drug research committees are inspected on a cyclical basis. DSI strives to inspect these entities every 2 to 3 years. For drugs, DSI's strategy for selecting clinical investigators for inspection is tied to the NDA. When an NDA is submitted to FDA for approval to market a drug product, clinical studies considered important to the approval of the product are selected for review (for-cause or routine) by the DSI staff or through consultation between DSI staff and medical officers responsible for reviewing NDAs. Responsibility for determining such important studies, according to FDA's Staff Manual Guide, rests with the appropriate drug review division. However, a change in that guide, in the final stages of approval as of April 1988, places this responsibility jointly on DSI and the drug review division. The manual had gotten out-of-date, according to the Deputy Director of DSI, and was being changed to reflect actual practice.

For biologics, prior to 1985 clinical studies were selected for review when the studies were completed, whether or not an application had been submitted. At the time of our review, DSI's strategy for reviewing clinical studies involving biologics was tied to the licensing application process for biologics. (The responsibility for biologics shifted from DSI in late 1987, as discussed on p. 8.)

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## Accuracy and Completeness of Data on Clinical Investigators, Institutional Review Boards, and Laboratories

FDA has regulations requiring drug sponsors to report to it the names of clinical investigators, toxicology laboratories, and institutional review boards used in studying drugs. FDA maintains these names in computerized inventory listings and uses the inventories of review boards and laboratories in selecting entities for inspection. Our review of correspondence files and discussions with both DSI officials and inspection officials in FDA's district offices indicate that they believed the inventories of institutional review boards and toxicology laboratories were sufficiently complete and accurate for scheduling inspections. District office officials told us they rarely discover an institutional review board or laboratory that was not in the inventory. While we did not independently assess the accuracy of these inventories, we have no reason to believe, from our discussions with DSI and district office officials and our review of correspondence and other records relating to the inventories, that they are not adequate.

FDA uses its inventory of clinical investigators, which includes studies they have performed, not to schedule inspections but to identify other studies by an investigator whose work has been questioned. FDA also may use the inventory to schedule additional studies for review or to notify sponsors that work by this investigator will not be accepted as a basis for approving new drugs.

In the past, FDA had problems maintaining an accurate, current inventory of clinical investigators. As of July 1986, according to a Center for Drugs and Biologics official, there was a 9-month backlog of clinical investigator data awaiting computer entry. Since we began our review, however, FDA has taken steps to improve the accuracy and completeness of the clinical investigator database. The FDA regulations were changed to make it easier for FDA staff to identify clinical investigators. Also, the Center increased the number of staff responsible for maintaining the database. Due to these efforts, DSI officials told us, the backlog has been eliminated and the database is now much more reliable. In view of FDA's actions to identify and correct deficiencies in its clinical investigator inventory, we did not determine whether there were still problems with it.

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## Oversight of Clinical Investigators, Review Boards, and Laboratories

The strategy for selecting laboratories, institutional review boards, and clinical investigators for review and inspection as discussed on page 13 appears appropriate in view of limited FDA resources available for reviewing and inspecting such entities. We concluded this after discussions with DSI officials but we did not verify that this strategy was always being followed.

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## Policy for Reviewing Important Studies Supporting New Drug Applications

DSI reviews the work done by approximately 200 to 300 clinical investigators annually. Each review covers one or more clinical studies performed by these investigators. It has been DSI's policy to review at least two important clinical studies for each NDA submitted to FDA, according to DSI officials.

The number of studies reviewed can vary, DSI told us, and it does not inspect every important study supporting an NDA. If a drug is intended for more than one indication (an intended use of the drug, as stated in the NDA), DSI selects at least two studies for each indication, according to a DSI official. Thus, for a drug with three intended uses, DSI will select at least six studies for review. In addition, if an NDA is supported by a large number of small clinical studies, DSI will review enough studies to obtain an adequate number of patients to assure that the studies were properly conducted.

In four of the six drug review divisions, directors and medical officers told us that they either jointly selected the clinical investigators for review in consultation with DSI or, in some cases, told DSI which investigators' work to review. In the two remaining divisions, medical officers did not select the studies to be reviewed, they said, nor did they coordinate with DSI in this selection.

After DSI completes its analysis of clinical investigator review findings, according to the FDA Staff Manual Guide, it recommends to the drug review divisions what actions it considers appropriate in terms of approving the drug. The drug review divisions are required to give "due consideration" to these recommendations in their safety and efficacy determinations.

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## Communication Between DSI Staff and Medical Officers Needs Improvement

Communication between DSI and the medical officers in the drug review divisions as to both selection of studies for review and utilization of results should be improved. Several of the medical officers we interviewed said they did not select, nor coordinate with DSI to select, studies for review. Review division files generally did not include results of DSI's reviews of studies, although DSI records show that copies were sent, nor did some medical officers remember being informed of review results. As a result, the method of selecting studies varied, and there was no assurance that the most important studies were being reviewed or that the results were taken into consideration in the decision to approve drugs for marketing.

In one case, DSI scheduled and reviewed 17 clinical studies of one drug, yet only one was considered important, according to the drug review division. The medical officer responsible for reviewing that drug for marketing approval did not know why DSI reviewed so many studies, he said, nor why they chose those studies to review, because DSI did not consult with him. The DSI staff person responsible for this drug is no longer with the agency. Another medical officer, who had been reviewing NDAs for 7 years, told us he would not release an NDA file to DSI because he did not know who DSI was or what responsibilities it had in the review process.

Once a review is completed, the district office submits the inspection report to DSI, which generally sends a "classification letter" to the inspectee. This letter informs the inspectee of the results of the review, points out any problem areas found by FDA inspectors, and outlines actions FDA expects the inspectee to take to correct the problems. To notify the review divisions of the results of each review, DSI sends copies of each classification letter to (1) the review division, (2) the responsible medical officer, and (3) the NDA file. Of the 190 reviews assigned for the drugs in our sample, however, only 27 classification letters or other written evidence of the results of the reviews were in the NDA or other files maintained by the drug review division relating to that NDA.

Some medical officers did not remember seeing the classification letter. Although some medical officers advised us that they had been informed of the results of DSI reviews by telephone, we found no documentation of these calls in the NDA files. Others did not remember being informed of the results of DSI reviews. As a result, we were unable to determine whether division directors and officials of the Office of Drug Research and Review, who had been delegated authority for approving most drugs, had the benefit of DSI's input when making approval decisions.

Although the drug review divisions are required to give due consideration to DSI's findings, DSI input is not required as part of NDA decision packages. The Director of the Office of Drug Research and Review told us that including DSI's findings in the decision package was a good idea. There was often some mention of DSI's input, he said, but only two of the six divisions generally included the results of DSI's review in the package. He also told us that the information forwarded in the decision package does not remain intact after the decision is made. It is returned to the review division and refiled in the NDA file.

## Enforcement Actions Initiated as Result of DSI Inspections

About 2 percent of the over 5,400 inspections completed by DSI between fiscal years 1977 and 1987 resulted in regulatory action against the inspectees by FDA (see app. II). These actions included disqualifying or suspending clinical investigators, disallowing the results of clinical or laboratory studies in support of NDAs, or prosecution. In addition, over 60 percent of DSI's inspection results indicated the need for corrective action by the inspected entity. These actions, considered voluntary by FDA, ranged from immediate correction of minor problems that could be easily handled to, in the most serious cases, a written explanation of actions that would be taken to correct the deficiencies disclosed during the inspections.

Since 1977, DSI inspections have resulted in the disqualification, suspension, or restriction of 70 clinical investigators for fraudulent or poorly conducted clinical studies.

## DSI Reviewed Most Important Studies Supporting NDAs

For the 41 drugs included in our sample, DSI generally scheduled and completed reviews of clinical studies, where appropriate. The number of reviews that DSI scheduled for these drugs is shown in table 2.1.

**Table 2.1: Number of Reviews Scheduled for 41 Drugs in GAO Sample**

Reviews scheduled	No. of drugs
0	10
1	6
2	5
3 or more	20
<b>Total</b>	<b>41</b>

For only 1 of the 10 drugs where no reviews were scheduled do we believe—and a DSI official agreed—that clinical studies should have been reviewed before approval. When the NDA on this drug was originally submitted, a DSI official told us, the district offices were assigned to review a selected number of clinical studies. Subsequently, the NDA was withdrawn by the sponsor, however, and DSI cancelled the reviews. When the NDA was resubmitted to FDA it “slipped through the cracks,” according to DSI. As to the other nine, DSI did not schedule clinical investigator reviews because:

- Four drugs were previously marketed products that FDA already had determined to be safe and effective,
- Four drugs had no clinical studies, and
- One drug was an “orphan drug”<sup>1</sup> with one-patient studies not conducive to review.

Of the six drugs that had only one review scheduled:

- Three had only one important clinical study;
- One had only one other important clinical study, conducted over 10 years earlier;
- One had one review scheduled for an isotope, a class of drugs that under current policy DSI normally does not review because it is not considered an important drug; and
- One had been marketed previously, but DSI believed that one clinical study should be reviewed, because the NDA was submitted for a significantly different dosage form.

For each of three drugs in our sample, at least two reviews were scheduled, but only one was completed:

- For one drug, the district office responsible for the reviews could not complete the assignments prior to drug approval because of its workload. Hence, two of the original three review assignments were cancelled when the drug was approved.
- For two other drugs, the district office attempted but could not complete one of two scheduled reviews. This can occur when a clinical investigator is no longer in the district, the clinical investigator dies, or the records to support the clinical study are no longer available. From the dates the drugs were approved, it appears DSI had sufficient time to assign other studies supporting the safety and efficacy of these drugs

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<sup>1</sup> A drug for a rare disease or condition.

for review. For one of the drugs, DSI could not explain why this did not occur; for the other, DSI concluded that the drug was of minor therapeutic importance and that only one of the two scheduled reviews was needed.

In 1985, when responsibility for biologics was transferred to DSI, the procedure for selecting important clinical studies of biologics for review was changed to take place when license applications were submitted to FDA for approval. Before that, review assignments were made when individual clinical studies appeared sufficiently complete to warrant a review, regardless of whether an application had been submitted to FDA. License applications for the six biologics we reviewed were submitted to FDA before DSI had responsibility for reviewing clinical studies of biologic products. For these six applications, at least two clinical studies had been reviewed for three applications and only one review had been completed for one other application. For the other two biologics, we could find no evidence of reviews of clinical studies.

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## More Timely Scheduling and Completion of Reviews Needed

In A Plan For Action, Phase II, dated May 1987, FDA announced a program to improve the premarketing evaluation processes for drugs. According to the plan, 3 years after the recruitment of additional required staff, FDA should be able to complete reviews of new drug applications in an average of 12 months compared with the then current average of 27 months. FDA has requested additional staff in its fiscal year 1989 budget.

For the 41 drugs included in our sample, FDA scheduled 190 reviews. Only 88 (46 percent) of the 190 were completed within 1 year of the date the NDA was submitted to FDA. For 73 of the remaining 102, FDA district offices were not notified of the need to make reviews for at least 1 year after receipt of the NDA. For four drugs in our sample, routine reviews of clinical investigator studies were completed after the drugs were approved. A number of reasons were given by DSI officials for the time required to schedule assignments. They advised us that under normal circumstances, routine assignments cannot be made to the district offices in less than two quarters (6 months) after the date the NDA is received by FDA because of the process DSI must follow. In contrast, for-cause inspections can be immediately assigned.

For routine inspections, on or about the 15th of each month DSI receives a list of NDAs received by FDA in the preceding month. Thus, as much as 6 weeks could elapse before DSI becomes aware of an incoming NDA. DSI

would like but does not have direct access to FDA's computerized management information system for tracking NDAs, a DSI official told us. Moreover, this official could not recall if such access had been requested. Direct access would allow DSI to be aware of incoming NDAs on a current basis. Once DSI knows of an NDA, it generally holds discussions with medical officers and selects studies for review. Materials—some of which must be obtained from the drug sponsor—are then assembled for the assignment package, which is sent to the district offices through the Office of Regulatory Affairs. That office requires that routine assignments be submitted 6 weeks before the start of any given quarter, DSI told us. The time is needed to get the assignments to the district offices before the beginning of the quarter, according to an Office of Regulatory Affairs official.

As a hypothetical example, if an NDA were submitted to FDA on January 2, DSI would not be aware of it until February 15. It then would need to determine which clinical studies to review. As assignments must be submitted to the Office of Regulatory Affairs by February 15 to be scheduled for the next quarter, the best DSI could do would be to include assignments on this NDA on the list to be submitted by May 15 for carrying out in the period July through September. Consequently, over 6 months could elapse before DSI schedules the studies for review by the district offices.

Also, the district offices may be unable to complete the assignments within the period assigned. For the drugs in our sample, the district offices completed 68 percent of the reviews assigned in the quarter and an additional 27 percent in the next quarter. Many of the reviews in our sample had been assigned to the district offices several years ago and might not reflect current problems with completing reviews.

In fiscal year 1986, DSI officials advised us, some district offices were having problems completing assignments. This was true, not only of reviews of drug studies by clinical investigators, but of other bioresearch monitoring inspections of toxicological laboratories, institutional review boards, and sponsor/monitors. For that reason, we determined the inspection dates for drug and biologics assignments sent to the district offices that year. At the time of our review, 562 had been completed. About 27 percent of the assignments were completed in the 3-month period assigned and about 74 percent within 6 months (see table 2.2). Inspections of clinical investigators were completed in about the same time as other bioresearch inspections. We found 24 percent completed in the 3-month period assigned and 70 percent within 6

months, with 30 percent requiring from 7 months to over a year to complete.

**Table 2.2: Time to Complete Bioresearch Monitoring Inspections** (Fiscal Year 1986)

Time to complete	Clinical investigators		Other inspections		Total inspections	
	No.	Percent	No.	Percent	No.	Percent
Within 3 months	57	24	92	29	149	27
Over 3-6 months	111	46	156	48	267	47
Over 6-9 months	42	18	49	15	91	16
Over 9 months-1 year	15	6	13	4	28	5
Over 1 year	15	6	12	4	27	5
<b>Totals</b>	<b>240</b>	<b>100</b>	<b>322</b>	<b>100</b>	<b>562</b>	<b>100</b>

For our review, we visited three district offices to discuss the bioresearch monitoring program. The three districts had comparable clinical investigator workloads in fiscal year 1986. Total bioresearch monitoring workload, however, varied from moderate to one of the highest of all FDA districts. District officials said that one reason they did not always complete assignments in a more timely manner was because they were involved in higher priority work, such as the investigation of product-tampering incidents.

Timeliness could be improved and staff time significantly reduced, officials in two districts told us, if FDA permitted abbreviated inspection reports when no major problems were noted. Nearly half of the inspectors' time and a significant amount of clerical support time go into preparing a detailed report of the inspection results, according to one district official, who said that most of that time could be saved. FDA already allows abbreviated reports in other programs, such as good manufacturing practice inspections, if no problems are found or violations uncovered are minor. Some long inspection reports we reviewed contained few, if any, adverse findings. The Office of Regulatory Affairs was considering allowing district offices to prepare abbreviated reports for bioresearch inspections, according to an office official.

## Conclusions

More timely scheduling and completion of reviews of clinical investigators would provide greater assurance that the clinical studies FDA uses as a basis for approving drugs are valid. Some scheduled reviews were never completed, we found, and others were completed after the drug was approved. FDA lacks goals and time frames for completing these reviews. Because of possible effects the reviews of a clinical investigator

can have on the approval of an NDA, it is particularly important that these reviews be completed more expeditiously. This is especially true if FDA is to achieve its plan for action on NDAs within 12 months, yet have the results of these reviews considered in the approval decision. Less than half of the reviews scheduled by DSI for the drugs in our sample were completed within 12 months of the date FDA received the NDA. The principal reason was the time taken to send the assignments to FDA's district offices. Of the clinical investigator reviews assigned to district offices in fiscal year 1986, 30 percent required from 7 months to over a year to complete after assignment.

Giving DSI direct access to information on incoming NDAs, revising the method of scheduling reviews, and allowing abbreviated reporting for all bioresearch monitoring inspections when inspectees are in substantial compliance should improve timeliness and conserve inspection resources.

In addition, communication and coordination between DSI and the review divisions should be improved. Studies to be reviewed should be jointly selected by DSI and the medical officers. FDA should better assure that the review divisions are made aware of the inspection results. Copies of classification letters frequently were not in the NDA files, and there was no documentation of telephone contacts.

Finally, DSI's input should be formally documented in decision packages for drugs approved at both the division level and the Office of Drug Research and Review level. Formal disposition of problems DSI finds with the conduct of clinical studies also should be documented as part of the NDA approval.

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## Recommendations to the Secretary of HHS

To enable FDA to carry out its bioresearch monitoring responsibilities in a more timely manner, we recommend that the Secretary of HHS require the Commissioner of FDA to

- finalize procedures in the Staff Manual Guide for selecting clinical studies for review and include provisions for communicating the results to officials responsible for reviewing new drug applications,
- give DSI direct access to FDA's automated management information system on incoming NDAs to facilitate inspection scheduling,
- establish goals or time frames for scheduling and completion of inspections prior to the approval of an NDA,

- 
- change the current quarterly assignment system so that clinical investigator inspections are assigned to district offices in a more timely manner,
  - allow district offices to write abbreviated inspection reports when inspectees are in substantial compliance with FDA requirements, and
  - require that a statement concerning the results of DSI's inspections be included in all new drug application approval packages and that inspection classification letters be included in the NDA file.

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## Agency Comments

By letter dated July 28, 1988, HHS concurred with all our recommendations (see app. III) and pointed out actions it was taking in response to the recommendations. Specifically, FDA stated that it

- has finalized the Staff Manual Guide, which was to be issued by August 31, 1988;
- has given DSI direct access to its automated management information system on new drug applications and is expanding these capabilities with the planned acquisition of additional equipment;
- is evaluating the current activity for scheduling and completing inspections to determine appropriate goals and time frames;
- has changed the system of scheduling inspections, beginning with the fourth quarter of fiscal year 1988, by providing that all bioresearch inspection assignments will be sent directly to the affected district office and making assignments immediately rather than waiting until the end of the quarter;
- has already implemented abbreviated reporting for inspections of institutional review boards and will incorporate the criteria for abbreviated reporting on inspections of clinical investigators into its fiscal year 1989 bioresearch monitoring compliance programs; and
- will issue the appropriate policy statement to require the results of DSI's inspections to become part of all new drug application decision packages and inspection classification letters to become part of the NDA file. In cases where no DSI inspections were conducted, the decision packages will include a notation that the application was not subject to DSI inspection.

# Results of For-Cause Inspections Unaffected by DSI Participation

Whether or not staff of the Division of Scientific Investigations directly participated in for-cause reviews and inspections of clinical investigators and sponsor/monitors made little difference in the results, our review of such inspections done between fiscal years 1982 through 1986 showed. Thus, there appears to be little reason for concern over cases in which DSI staff are unable to directly participate. Of for-cause inspections for which such information was available, 64 percent were completed in the 3-month period assigned and 97 percent within 6 months.

Over the past 10 years, DSI has assigned or conducted over 400 for-cause inspections of clinical investigators and sponsor/monitors. As explained on page 9, for-cause inspections typically are performed because a clinical study is of particular importance to an NDA approval, there is some indication of wrongdoing, or a clinical investigator is conducting an unusually large number of studies. A DSI headquarters staff person is assigned responsibility for the inspection and often participates as part of the inspection team. There is no particular criteria for whether a DSI staff member should take part in an inspection, a DSI official explained. Participation depends on a number of factors including the work schedule of the DSI staff person and the assigned district investigator. DSI's "comfort level" with having district investigators perform the inspection without DSI participation, the official said, depends on the capability of the individual investigator.

In fiscal years 1982-85, DSI staff participated on average in about 74 percent of the 134 inspections conducted. In fiscal year 1986, however, DSI directly participated in only 53 percent of 47 inspections conducted. A DSI official told us that this was due to decreased resources and travel funds. In fiscal year 1987, however, DSI participation rose to 71 percent of 38 inspections. A DSI official explained that there was less pressure in fiscal year 1987 to not expend travel funds than in fiscal year 1986.

## Violation Findings No More Serious When DSI Staff Participated

To determine if there was a significant difference in the results when DSI staff were part of the inspection team, we analyzed the results (classification) of all for-cause clinical investigator and sponsor/monitor inspections conducted during fiscal years 1982-86. Participation by DSI staff, because of their expertise and particular knowledge of the drugs, might make a difference in inspection findings and types of actions recommended; thus we used the severity of the classification of inspection results as criteria. Of the 181 for-cause inspections conducted during the period, DSI staff directly participated in 124, or 69 percent. An analysis of the results showed little difference in the severity of violations found

**Chapter 3**  
**Results of For-Cause Inspections Unaffected**  
**by DSI Participation**

and types of actions recommended when DSI staff participated and when they did not.

Of the 124 inspections in which DSI participated, 16 percent were classified “official action indicated,” 64 percent as “voluntary action indicated” (violations ranging from minor oversights to those requiring a written action plan of corrective measures), and 20 percent as “no action indicated” (inspectee in compliance) (see table 3.1). This compares closely to 19, 56, and 23 percent in these categories, respectively, for the 57 inspections in which DSI did not participate.

**Table 3.1: DSI Participation in For-Cause Inspections** (Fiscal Years 1982-86)

Classification	DSI participation		No DSI participation		Total	
	No.	Percent	No.	Percent	No.	Percent
Official action indicated	20	16	11	19	31	17
Voluntary action indicated	79	64	32	56	111	61
No action indicated	25	20	13	23	38	21
Other	0		1	2	1	1
<b>Totals</b>	<b>124</b>	<b>100</b>	<b>57</b>	<b>100</b>	<b>181</b>	<b>100</b>

FDA further divided most of the inspection results classified as “voluntary action indicated” into subcategories. Even within this category, the violations were about the same when DSI staff participated and when they did not. Overall, DSI participated in 79 (71 percent) of the 111 inspections where voluntary action was indicated. They took part in 73 percent of the inspections in the most serious subclassification and 72 percent of the less serious.

Most directors of FDA’s drug review divisions believed they lacked a basis to comment on the district offices’ ability to conduct inspections. But one told us, when asked his “comfort level” with the inspections, that DSI staff are needed for the scientific aspects of clinical studies because of their scientific expertise. DSI believes that its staff bring to the inspection team both added expertise and a broader knowledge of all of the inspection activity on any given drug.

According to officials in the three district offices we visited, DSI added scientific expertise and brought some additional insight on each drug to the inspection team. Only one official, however, thought that DSI should be present during the inspection.

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Officials in two districts told us that coordinating the assigned district inspector's schedule with DSI and the clinical investigator or sponsor/monitor to be inspected sometimes was a problem and lengthened the time needed to complete inspections.

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## Conclusions

DSI staff may bring additional expertise and a broader perspective to the inspection team. But our analysis of for-cause clinical investigator and sponsor/monitor inspections in fiscal years 1982-86 showed that there was little difference in the severity of the findings whether DSI staff participated in the inspection or not. Thus, there appears to be little reason for concern in those cases in which DSI staff are unable to participate. Participation by DSI staff, however, should be encouraged so they can maintain their knowledge about particular drugs and better interact with medical officers in the drug review divisions. A majority of for-cause inspections during this period were completed in the period assigned and almost all were completed within 6 months.



# Bioresearch Inspections Completed by FDA (Fiscal Years 1977-87)

Fiscal year	Subject of inspection <sup>a</sup>						Totals
	Clinical investigators		Sponsor/ monitors	Laboratories	Institutional review boards	Radioactive drug research committees	
	For-cause	Routine					
1977	4	36	b	0	101	0	141
1978	32	33	b	0	220	0	285
1979	63	146	b	6	225	15	455
1980	57	235	b	54	256	27	629
1981	42	225	b	58	240	25	590
1982	18	179	19	59	210	21	506
1983	40	187	17	59	246	20	569
1984	29	222	18	81	241	19	610
1985	39	171	19	69	230	20	548
1986	45	164	26	80	206	18	539
1987	36	229	17	81 <sup>c</sup>	212 <sup>c</sup>	17 <sup>c</sup>	592 <sup>c</sup>
<b>Totals</b>	<b>405</b>	<b>1,827</b>	<b>116</b>	<b>547</b>	<b>2,387</b>	<b>182</b>	<b>5,464</b>

<sup>a</sup>Numbers do not include inspections attempted but not completed.

<sup>b</sup>Sponsor/monitor inspections were included in clinical investigator inspections until fiscal year 1982.

<sup>c</sup>Does not include 3 laboratory, 22 institutional review board, and 1 radioactive drug research committee inspections not classified as of January 1988.

# Classification of Bioresearch Inspections (Fiscal Years 1977-87)

Fiscal year	Classification of inspection results				Totals
	Official action	Voluntary action	Other	No action	
1977	2	50	0	89	141
1978	12	67	2	204	285
1979	24	144	6	281	455
1980	10	230	2	387	629
1981	14	254	3	319	590
1982	5	381	0	120	506
1983	11	453	0	105	569
1984	9	471	0	130	610
1985	8	467	1	72	548
1986	11	438	0	90	539
1987	12	454	0	126	592
<b>Totals</b>	<b>118</b>	<b>3,409</b>	<b>14</b>	<b>1,923</b>	<b>5,464</b>
Percent	2.2	62.4	2	35.2	100

# Comments From the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

JUL 28 1988

Mr. Lawrence H. Thompson  
Assistant Comptroller General  
U.S. General Accounting Office  
Washington, D.C. 20548

Dear Mr. Thompson:

Enclosed are the Department's comments on your draft report, "FDA's Reviews of New Drugs: Changes Needed in Process for Reviewing and Reporting on Clinical Studies." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "R. Kusserow".

Richard P. Kusserow  
Inspector General

Enclosure

Appendix III  
Comments From the Department of Health  
and Human Services

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES  
ON THE GENERAL ACCOUNTING OFFICE DRAFT REPORT, "FDA'S REVIEWS OF  
NEW DRUGS: CHANGES NEEDED IN PROCESS FOR REVIEWING AND REPORTING  
ON CLINICAL STUDIES" REPORT NO. HRD-88-100, JUNE 1988

We appreciate the opportunity to review the draft report. Generally, we find it to be accurate and fair. We have the following comments with regard to the recommendations.

GAO Recommendation

To enable FDA to carry out its bioresearch monitoring responsibilities in a more timely manner, GAO recommends that the Secretary of HHS require the Commissioner of FDA to:

- Finalize the Staff Manual Guide establishing procedures for selecting clinical studies for review and include provisions in the guide for communicating the results of the inspections to the officials responsible for reviewing new drug applications.

Department Comment

We concur. The Staff Manual Guide has been finalized and will be issued to FDA reviewing divisions by August 31.

GAO Recommendation

- Provide DSI direct access to FDA's automated management information system on incoming NDA's to facilitate the inspection scheduling process.

Department Comment

We concur. The Division of Scientific Investigations (DSI), FDA, currently has the capability to directly access FDA's automated management information system (MIS) on new drug applications (NDA). This capability is being expanded, with the planned acquisition of additional microcomputers, modems, and high-speed equipment for accessibility and dissemination of data.

As noted by GAO, the NDA reviewing divisions currently participate in identifying specific clinical trials that need to be inspected. This can only be done after at least a preliminary review of the application has been done and decisions reached about which studies are pivotal, whether the data appear to be valid, the significance of the new drug, and other similar factors. Furthermore, some 30 to 40 percent of applications received do not reach approval for reasons other than those

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Comments From the Department of Health  
and Human Services

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associated with inspections of clinical investigations. We believe the practice of involving reviewing decisions in the decision-making is necessary and will continue to do so. This will reduce the impact of direct MIS access on scheduling inspections.

GAO Recommendation

- Establish goals or timeframes for when inspections should be scheduled and completed prior to the approval of an NDA.

Department Comment

We concur. The FDA is evaluating the current activity to determine the appropriate goals and time frames for scheduling and completing inspections of clinical investigators. It should be noted, however, that completion of inspections has not been a controlling factor in the time required for new drug reviews. In most cases, the inspections have been completed well before a final decision was made regarding the new drug application. As efforts to reduce review time are achieved, FDA will continue to monitor closely the scheduling of inspections to assure that they do not impede the progress of new drug reviews.

Further, it should be noted that goals and time frames will always have to be sufficiently flexible to accommodate critical human safety priorities performed by FDA district offices, particularly emergencies such as product tampering, life-threatening product contamination incidents, and other similar events.

GAO Recommendation

- Change the present quarterly assignment system to allow sending clinical investigator inspection assignments to district offices in a more timely manner.

Department Comment

We concur. Beginning with the fourth quarter of Fiscal Year (FY) 1988, all inspection assignments regarding FDA's bioresearch monitoring program will be sent directly to the affected district office rather than being routed through FDA's Office of Regional Operations (ORO) at headquarters. At the same time, assignments will be issued immediately rather than waiting until the end of the quarter as was the previous practice. In order to preserve management oversight of the program, ORO will also receive electronic notification of the assignments.

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Comments From the Department of Health  
and Human Services

Page 3

GAO Recommendation

- Allow district offices to write abbreviated inspection reports when inspectees are in substantial compliance with FDA requirements.

Department Comment

We concur. FDA has already implemented a procedure for inspections of institutional review boards and will incorporate the criteria for abbreviated reporting on inspections of clinical investigations into the FY 1989 bioresearch monitoring compliance programs for district offices.

GAO Recommendation

- Require that a statement concerning the results of DSI's inspections become part of all new drug application approval packages and that inspection classification letters become part of the NDA file.

Department Comment

We concur. FDA will issue the appropriate policy statement; however, not all NDA's are subject to DSI review. This was acknowledged by GAO in their review of FYs 1985 and 1986 NDA approvals (page 16 of the draft report). Applications for which no DSI inspections were conducted would not be affected by implementation of this recommendation. For these applications, the NDA approval packages and files will include a notation that the applications were not subject to DSI inspections.

Now on p. 11.



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