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

September 1986

DRUG REGULATION

FDA's Computer Systems Need to Be Better Managed

131277

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

Dear Mr. Chairman:

This report responds to your March 28, 1984, request that we review the Food and Drug Administration's management and use of drug information. We found that, although the agency has made some progress in improving its information systems, these systems are still neither completely reliable nor useful to the agency's drug reviewers. In addition, we expressed concern that the agency has not pursued an overall, systematic approach to managing its vast information resources.

This report includes recommendations to the Secretary of Health and Human Services. The agency was given an opportunity to comment on our draft report, and its comments are included.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its issue date. At that time, we will send copies to the Secretary of Health and Human Services; the Commissioner, Food and Drug Administration; the Chairmen, House Committee on Government Operations and Senate Committee on Governmental Affairs; and the Director, Office of Management and Budget.

Sincerely yours,

Daniel C. White
for Warren G. Reed
Director

Executive Summary

Purpose

Congressional hearings in 1982 and 1983 disclosed major problems in the Food and Drug Administration's (FDA) handling of drug information in two cases. In these instances, (1) critical data on adverse reactions were not entered into FDA's computer system, thus obscuring the extent to which a drug had caused adverse reactions, and (2) critical information concerning the safety of one drug was not reviewed before the drug was approved and marketed.

The Chairman, Subcommittee on Intergovernmental Relations and Human Resources, House Committee on Government Operations, was concerned about FDA's handling of information and asked GAO to determine whether FDA's primary drug information systems were

- accurate and complete and
- useful to reviewers in facilitating the evaluation of new drug applications.

To fully address the Chairman's concerns, GAO also assessed FDA's compliance with Office of Management and Budget (OMB) Circular A-130.

Background

Ensuring the safety and efficacy of the nation's drug supply is one of FDA's primary missions. The Center for Drugs and Biologics is FDA's regulatory arm over all drugs marketed in the United States. In performing this regulatory function, the Center's drug reviewers annually handle millions of documents related to the safety and efficacy of particular drugs.

To help reduce its paperwork burden and assist in drug regulation, the Center operates three principal automated systems. They are: (1) the Adverse Drug Reaction System, which maintains reports on adverse reactions to marketed drugs to support postmarket surveillance and the drug review process; (2) the Astro-IV Drug Information System, which contains scientific and historical data on new drug applications; and (3) the New Drug Evaluation/Management Information System, which is used mainly to identify the assigned reviewers and the amount of time an application has been undergoing review. The Center's top managers consider these systems critical to professional drug reviewers and management in evaluating new drugs and monitoring marketed drugs.

The Paperwork Reduction Act of 1980 requires that agencies manage their information activities in an efficient, effective, and economical manner. OMB Circular A-130 provides direction to federal agencies in

carrying out this requirement. Further, the Federal Information Resources Management Regulation requires a comprehensive automatic data processing requirements analysis, covering such critical factors as data entry, handling, and output needs, and the automatic data processing functions that must be performed to meet the mission need.

Results in Brief

Despite some improvements since 1983, FDA's three principal drug information systems are inaccurate and one is incomplete. In addition, these systems are not useful to most of FDA's drug reviewers because they are not reliable and do not meet their needs in facilitating the evaluation of new drug applications. These system inadequacies and other information management deficiencies may result in delays in identifying unsafe drugs that are already on the market and in the approval and marketing of new drugs that are unsafe, ineffective, or both.

FDA's difficulties with its drug information systems continue because the agency has not effectively managed its information resources, as required by OMB Circular A-130.

Principal Findings

Systems' Error Rates

FDA requires its drug information systems to be 100 percent complete and accurate. In contrast, GAO's statistical analysis showed that

- 35 percent of all reports in the Adverse Drug Reaction System contained inaccurate data,
- 17 percent of all new drug applications in the Astro-IV System contained inaccurate data,
- 34 percent of all new drug applications in the New Drug Evaluation/Management Information System contained inaccurate data, and
- 26 percent of adverse reaction reports received were not entered into the Adverse Drug Reaction System. (See page 20.)

Systems' Usefulness to Reviewers

Eighty-nine percent of drug reviewers never use the Astro-IV System, while 79 percent never use the Adverse Drug Reaction System. Reviewers said they did not use these systems primarily because the systems did not meet their needs. The specific deficiencies cited were problems with reliability, usefulness, and timeliness. Sixty-one percent

of the Center's managers use the New Drug Evaluation/Management Information System to track the progress of new drugs under review. However, because the system is not completely reliable, many managers supplement the system's output with information from individual automated and manual systems, resulting in duplicated efforts and wasted time. (See page 22.)

Information Resources Management

GAO found that inadequate quality-control procedures contributed to unreliable systems, detailed long-range automatic data processing plans were not developed, and requirements analyses and standardization efforts were limited. Although the Center has improved its information systems to alleviate problems, such as data entry backlogs, it has not conducted comprehensive requirements analyses in developing, implementing, or modifying drug information systems. (See page 29.)

In addition, FDA continues to have difficulties in managing its vast paper load. The document control rooms and drug reviewers' offices are swamped with paper—a situation that is detrimental to efficient and effective drug reviews. FDA is exploring the feasibility of acquiring new technology to assist in managing the voluminous documentation it must process yearly. The agency is testing a system that allows the review of clinical data from new drug applications through a terminal on a reviewer's desk. (See page 36.)

FDA's senior official for information resources management, who has held this position since 1981, has been unable to resolve the agency's considerable information management problems, largely because top management has provided insufficient organizational support. On August 2, 1985, the FDA Commissioner approved the establishment of a Division of Information Resources Management and appointed a director to run the new division and oversee the agency's information management activities. (See page 25.)

Recommendations

GAO recommends that the Secretary of Health and Human Services, through the Assistant Secretary of Management and Budget, direct the FDA Commissioner to take the following actions:

- Establish effective data input and processing controls.
- Identify and document reviewers' and managers' automation needs.
- Develop long-range automatic data processing plans.

Additional recommendations appear on page 41.

Agency Comments

GAO requested written comments on a draft of this report from the Department of Health and Human Services. Although the Department generally disagreed with GAO's findings, it concurred with all but one recommendation. Generally, the Department was concerned that certain agency documents and statements may have contributed to what it believes is an incorrect perception that specific information systems were intended to support the drug review process. In particular, the Department cited GAO's treatment of the Astro-IV System as its primary concern, a system that the Department maintains was not intended to support new drug reviewers. GAO disagrees; the evidence it obtained from FDA officials and documents strongly supports GAO's assessment of the purpose of FDA's drug information systems. However, in light of FDA's apparent confusion over the intended use of the Astro-IV System, GAO has changed its recommendation from requiring the agency to correct system errors to recommending that FDA perform a complete assessment of Astro-IV to determine its actual role in agency operations.

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Abbreviations

FDA	Food and Drug Administration
GAO	General Accounting Office
OMB	Office of Management and Budget

Introduction

Protecting and promoting the American public's health is the primary mission of the Food and Drug Administration (FDA). Under the direction of the Department of Health and Human Services, FDA is responsible for making sure that (1) food is safe, pure, and wholesome; (2) drugs for humans and animals, biological products, and therapeutic devices are safe and effective; and (3) radiological devices and procedures do not result in unnecessary exposure to radiation. To that end, FDA establishes food and product standards; evaluates the safety and efficacy of new drugs and biologics (blood products and vaccines); and monitors food, drugs, and electronic products to ensure that they are correctly labeled and are safe.

One major aspect of FDA's responsibilities—drug regulation—is carried out by the agency's Center for Drugs and Biologics. The Center is modest in size and budget but not in impact; its actions, such as approving new drugs, affect millions of people and the $18-billion pharmaceutical industry. The Center's full-time personnel number about 2,400, including chemists, pharmacologists, medical officers, biostatisticians, and supporting staff. Of the Center's total staff, 182 are drug reviewers who are responsible for reviewing, approving, and monitoring drugs. The Center's budget was $154 million in fiscal year 1985.

The Center's drug review and monitoring responsibilities have been delegated to three offices. The Office of Drug Research and Review and the Office of Biologics Research and Review are responsible for reviewing new drug applications for safety and efficacy, and for monitoring the adverse effects of marketed drugs. These offices have the authority to recommend approval of new drugs and to recommend a drug's recall should the need arise. A third office, the Office of Epidemiology and Biostatistics, is also responsible for monitoring adverse drug reactions; however, it does not have any regulatory authority. The office relies on the Reports Evaluation Branch, where reviewers develop detailed reports on drug side effects, to provide information to the offices having regulatory authority.

Over the years, the Center has developed automated systems to support its mission of approving new drugs and monitoring marketed drugs. Officials told us that reliable and useful computer systems are essential FDA tools because of the many pharmaceuticals and the sheer amount and complexity of information that the Center must process and analyze. In late 1985, the Secretary of Health and Human Services noted that a single new drug application often comprised up to 100,000 pages

of documentation and was delivered to FDA "literally by truck." The Secretary commented also that FDA, in an attempt to alleviate this avalanche of paperwork, was moving toward improved technology and automation.

The Paperwork Reduction Act of 1980 addresses the need to properly manage information and information technology in a federal agency. The act requires that agencies manage their information activities, to include automated systems and paper load, efficiently, effectively, and economically. Further, prior to a system's acquisition or augmentation, the Federal Information Resources Management Regulation requires a comprehensive automatic data processing requirements analysis, covering such factors as data entry, handling, and output needs, and the automatic data processing functions that must be performed to meet the mission need.

Regulatory Responsibilities of Drug Reviewers

Reviewers at the Center for Drugs and Biologics play a critical role in determining the safety and effectiveness of drugs—both before and after the drugs are placed on the market. The primary regulatory intermediaries between pharmaceutical companies' research and development activities and the marketplace, these reviewers receive approximately 1,800 investigational new drug applications,[1] 450 new drug applications, 3,500 supplements to new drug applications,[2] and nearly 40,000 adverse reaction reports[3] yearly.

Before new drugs are placed on the market, a reviewer must examine and approve applications submitted by pharmaceutical companies to attest to the drug's safety and efficacy. Clinical test results represent 80 percent of these usually voluminous applications.

The review process for new drugs requires the efforts of reviewers from at least three disciplines: (1) a chemist, who reviews the chemistry and the manufacturing controls and processes; (2) a pharmacologist, who reviews the animal test results for toxicology; and (3) a medical officer, who reviews the clinical test results for safety and efficacy. Although any one of these reviewers can recommend approving or disapproving a

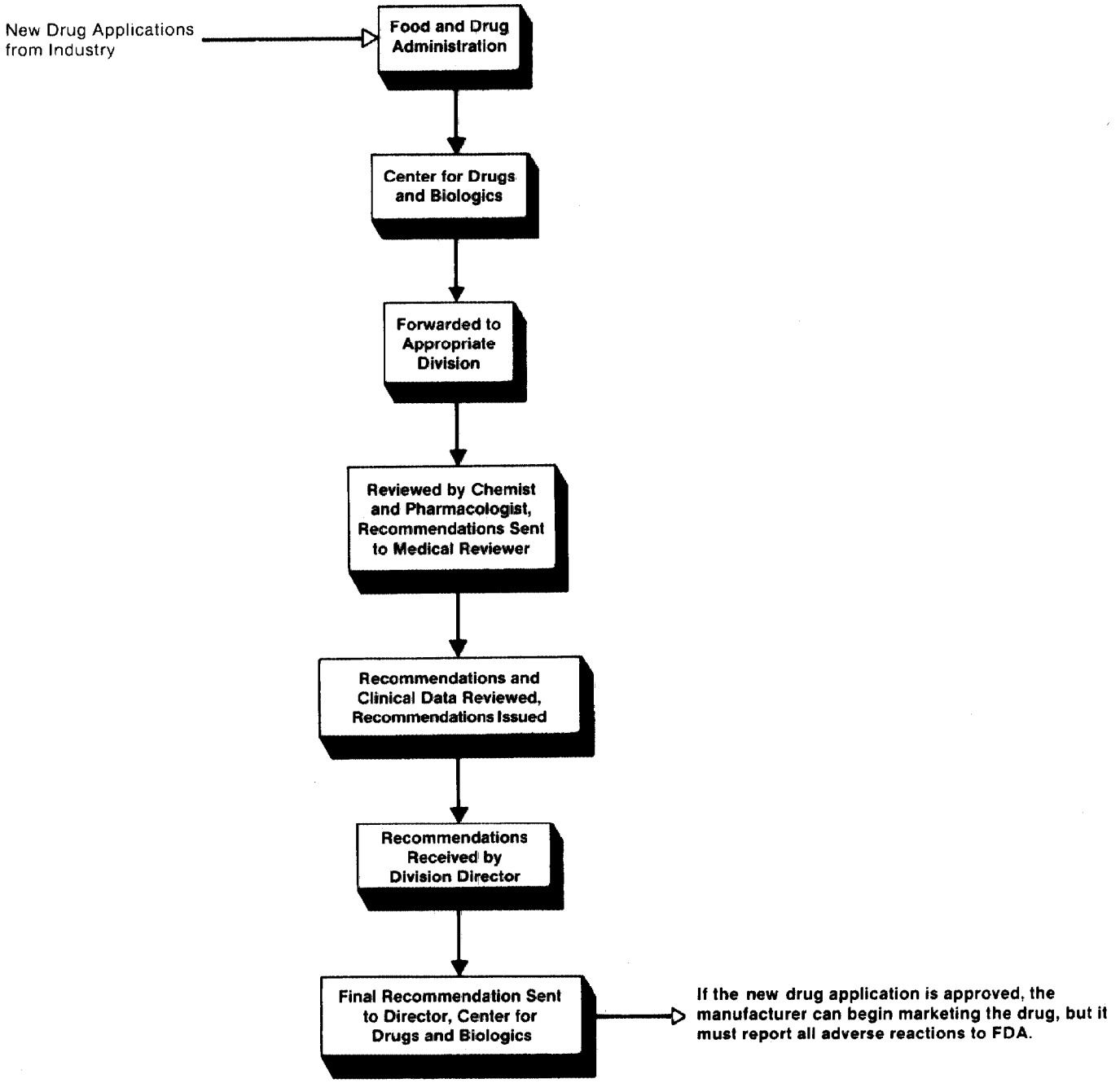
[1] An investigational new drug application is usually a request for FDA to approve clinical testing of promising chemical compounds in humans.

[2] A supplement is a proposal to change an approved drug application in terms of its formula, manufacturing process, labeling, packaging, and prescribed use.

[3] An adverse drug reaction report describes the undesirable side effect caused by a drug.

new drug, the medical officer is normally responsible for making the final recommendation on a new drug application and for writing the Summary Basis of Approval. Figure 1.1 traces the decision process for reviewing new drug applications.

Figure 1.1: Decision Process for New Drug Applications



In addition to approving new drugs for marketing, FDA is responsible for monitoring adverse drug reactions as they occur throughout the nation. Specialists and medical reviewers perform this important function. A newly approved and powerful medicine to treat acne illustrates how the adverse drug reaction monitoring process works. Following the drug's approval and marketing, both the manufacturer and FDA scrutinized the reports on adverse reactions. They discovered that severe headaches were linked to the drug, a previously unknown reaction. The company changed the label and the package insert to warn consumers, and FDA issued a memorandum informing doctors and hospitals of the newly discovered side effect.

According to an FDA official, because of the many unknown factors surrounding a new drug, it is critical to the nation's health for reviewers to take immediate action when the number of adverse drug reactions reported is significant. He added that a timely and accurate automated information system is essential to helping reviewers quickly identify approved and marketed problem drugs. For example, a reviewer could use an automated system to obtain statistics on the number and frequency of certain types of reactions to a drug. Without a computer, a reviewer must manually read and count each of the adverse reaction reports forwarded by the drug manufacturer.

Center for Drugs and Biologics Operates Major Computer Systems to Assist in Drug Reviews

In performing its regulatory function, the Center handles millions of pages of documentation each year. These documents range from single-page adverse drug reaction reports to 600-volume new drug applications. Center officials stated that before the 1960s, new drug applications comprised little documentation. The amount of documentation multiplied when the 1962 amendments to the Federal Food, Drug and Cosmetic Act required that drugs be determined effective as well as safe, and when FDA required companies to include all clinical test results with their applications.[4] Because of publicity, general concern about better health, increased awareness of drugs' potential side effects, and continuing adverse drug reactions, doctors, hospitals, and pharmaceutical companies report nearly 40,000 adverse drug reactions to FDA annually. Additionally, the Center internally generates thousands of documents, reports, and letters yearly. To help reduce its paperwork

[4]New regulations published December 7, 1984, limited the requirement for clinical case reports to specific instances where "a more detailed review is necessary." FDA estimates that this approach will result in a 75-percent reduction in the number of case reports being submitted; however, several FDA managers indicated they would request clinical reports in most instances.

burden and assist in the drug review process, the Center operates several computer systems, three of which are described below.

Astro-IV Contains Automated Information for Reviewers

To support the efficient and accurate review of new drugs, the Center provides reviewers access to its scientific drug information system, called Astro-IV. According to FDA, Astro-IV is intended to provide reviewers with such critical information as drug names (generic and trade), manufacturers, active and inactive ingredients, pharmacological activity, dosage forms, and approval dates. Astro-IV includes data on 22,000 new drug applications—of which 8,700 are active—and 25,000 investigational new drugs.

According to Center officials, Astro-IV contains large amounts of historical and scientific information. One of the system's major capabilities is to provide lists of drugs containing specific ingredients. For instance, if chemists were concerned about the presence of sodium chloride in a new drug, they could request from Astro-IV a list of all drugs that contain the ingredient. They could then compare the structures of those drugs with the new drug under review to find possible similarities or irregularities.

Adverse Drug Reaction System Assists in Postmarket Drug Surveillance

To support its postmarket surveillance of new drugs, FDA has developed a computer system to store and analyze adverse drug reaction data, the Drug Experience Information System, more commonly known as the Adverse Drug Reaction System. The Center's Division of Drug and Biological Product Experience can enter into or extract from the system such information as drug names, reactions, manufacturers, and dosages. Information from this system assists FDA in issuing alerts on marketed drugs and, if necessary, in withdrawing approval from manufacturers to market these drugs.

The Adverse Drug Reaction System is designed to allow reviewers to link adverse reactions to specific drugs and to track the frequency of these reactions over time. The system is intended to free reviewers from handling hundreds of reports and allow them more time for analysis. Agency officials told us that the system's reliability and utility were closely linked to FDA's ability to monitor and control marketed drugs.

New Drug Evaluation/ Management Information System Provides Automated Support to Managers

FDA's drug regulatory responsibilities require the constant attention of mid- and upper-level management. These managers are responsible for ensuring that the Center's professional staff thoroughly and expeditiously review new drug applications. In addition, they must be able to respond to information requests from the pharmaceutical industry, consumer groups, and the Department of Health and Human Services.

To assist in monitoring and tracking new drug reviews, the Center provides directors, managers, and supervisors immediate access to the New Drug Evaluation/Management Information System. This system provides such information as the case number for a new drug application, trade name, reviewers assigned, and time elapsed since receipt.

According to FDA officials, the information from this system should support two management concerns. First, to expedite the review process, management must be able to parcel out the drug review work load rationally and equitably. Second, to monitor and expedite the review process, management must be aware of the time each new drug has been under review. Within 180 days after a new drug application is filed (unless FDA and the drug manufacturer agree to a delay), FDA must approve the application or give the applicant notice of an opportunity for a hearing on the deficiencies found. Center officials said that the New Drug Evaluation/Management Information System should provide management with accurate and complete information on the status of new drug applications and the work load of reviewers.

Past Concerns About FDA's Management of Drug Information Systems

Over the past few years, we, along with the Congress, have expressed concern about FDA's management of its three drug information systems.

We stated in a 1980 report[5] that most drug reviewers were aware of Astro-IV but seldom used it. In addition, the same report noted that drug reviewers were concerned that the New Drug Evaluation/Management Information System did not contain the appropriate type of information, such as generic drug nomenclature, cross-indexed to trade names. In another report,[6] we indicated that drug processing time, a data element in the New Drug Evaluation/Management Information System, could not

[5] FDA Drug Approval - A Lengthy Process That Delays the Availability of Important New Drugs (HRD-80-64, May 28, 1980).

[6] Speeding Up the Drug Review Process: Results Encouraging, But Progress Slow (HRD-82-16, Nov. 23, 1981).

be used to monitor FDA's progress in approving new drugs because the system was unreliable.

In 1982[7] we reported that the Adverse Drug Reaction System was beset with problems; only 44 percent of adverse drug reaction reports received were actually entered into the computer. In addition, we noted that the time required for data entry was excessive. We also reported that the system was inflexible and seldom used and that a large backlog of unprocessed reports existed.

In 1983 hearings, the Congress identified major problems regarding FDA's handling of information on two drugs. Congress was concerned when FDA could not reconcile its records with the number of adverse reactions to a brand name drug—Zomax—reported by the drug manufacturer. The manufacturer reported sending 900 adverse drug reaction reports, but FDA could account for only 300 in its computer. The hearings also disclosed that in 1982 FDA had not adequately reviewed critical safety information in its possession before approving a similar drug, Oraflex, for marketing. In addition, according to the hearings, several deaths were attributed to the use of these drugs, and both manufacturers withdrew them from the market. In these cases, (1) critical data were not entered into computer systems, thus preventing reconciliation of numerous adverse reactions and obscuring the problem's extent and (2) critical information, although available to FDA, was not adequately reviewed before one drug was approved.

Because of the problems noted above, the Congress questioned FDA's ability to manage reported information in reviewing, approving, and monitoring drugs.

Objectives, Scope, and Methodology

After the 1983 congressional hearings, the Chairman of the Subcommittee on Intergovernmental Relations and Human Resources, House Committee on Government Operations, asked us to undertake a comprehensive review of the manner in which FDA collects, processes, uses, and disposes of information.

In subsequent discussions with the Chairman's office, it was agreed that we would structure our audit to (1) focus on the FDA office responsible for drug regulation, the Center for Drugs and Biologics, and (2) assess

[7] FDA Can Further Improve Its Adverse Drug Reaction Reporting System (HRD-82-37, Mar. 8, 1982).

the reliability and utility of the Center's information systems in facilitating the prescription drug review process.

Our audit focused on three areas: data system reliability/utility, technology, and information resources management. We chose to review three of four information systems FDA personnel identified as critical to supporting the new drug evaluation process: the Adverse Drug Reaction System, Astro-IV, and the New Drug Evaluation/Management Information System. We did not review the Drug Registration and Listing System because it had little relation to new drug reviews or to the monitoring of existing drugs. Our audit approach was to evaluate the reliability of the three systems and to discuss their utility with managers and reviewers responsible for approving new drugs, monitoring adverse drug reactions, and accomplishing drug regulation. We did not assess how these systems support the review of investigational new drug applications.

We discussed FDA operations with officials from FDA headquarters. We also interviewed officials at eight drug manufacturing companies, officials from an information research company involved in an experiment to electronically submit new drug applications to FDA, and federal and private-sector officials who have automated their operations, to determine whether any of their ideas might technically assist FDA's operations.

To determine whether individual systems were accurate and complete, we also conducted system reliability tests and user surveys. (Confidence levels of our statistical reliability tests are shown in appendix I.) The Astro-IV[8] and Adverse Drug Reaction systems were tested for accuracy by comparing a statistically valid, random sample of new drug application source documents with data from the computer. We tested the accuracy of the New Drug Evaluation/Management Information System by checking the reliability of reviewer work load and new drug application assignment data. We selected a sample of 48 of the 182 new drug application reviewers and obtained print outs that showed the new drug applications and supplements assigned to each of the sampled reviewers. We then interviewed each reviewer, when possible, to determine whether applications and supplements were assigned as indicated on the print outs. We conducted completeness tests for Astro-IV and the New Drug Evaluation/Management Information System by taking a random sample of new drug applications and checking the computer's data base to determine if the documents had been entered. We tested the

[8]Our test sample and universe for Astro-IV only included active new drug applications.

Adverse Drug Reaction System by taking a random sample of adverse reactions from drug review document rooms; we then checked the data base to determine if the documents were entered.

Using a structured interview, we conducted a survey of 102 FDA users on a statistically valid, random sample basis. Our sample included 10 adverse drug reaction reviewers from the Reports Evaluation Branch, comprising the entire staff. In addition, we interviewed 62 of the 182 medical officers, chemists, and pharmacologists who review new drug applications. We also interviewed 30 of the 78 directors, supervisors, and consumer safety officers responsible for managing the drug review process; this sample included all 6 drug review division directors. We analyzed the interview results to determine whether existing information systems were being used and whether an adequate needs assessment was conducted before the systems were developed.

Finally, we assessed FDA's information resources management procedures and evaluated whether they adequately assisted the agency in implementing and managing automatic data processing systems and technology. As part of this effort, we interviewed upper-level management and discussed the need for organizational change.

We conducted our work at FDA and Public Health Service offices in Rockville, Maryland, and at the Department of Health and Human Services in Washington, D.C. We also visited medical computer research companies and pharmaceutical firms in several locales. We performed our review in accordance with generally accepted government auditing standards.

FDA's Drug Information Systems Have Been Upgraded, but Problems Remain

Although FDA's Center for Drugs and Biologics has improved its three major drug information systems, serious problems remain. All three systems contain significant error rates, and one is incomplete. In addition, the majority of FDA reviewers are not using the systems because they are not reliable and do not adequately support the drug review process. Although the Center is completing its reviews without these systems, the fact that computer technology is available but is not accurate, complete, or being extensively used, raises questions about the efficiency and effectiveness of FDA's operations. FDA's continued reliance on manual systems to review large amounts of complex data carries the risk that important information could be lost or missed during the review process. These inadequacies may result in delays in identifying unsafe drugs that are already on the market and in the approval and marketing of new drugs that are unsafe, ineffective, or both.

FDA Has Made Some Improvements in Its Information Systems

Following congressional hearings criticizing its management of information systems, the Center attempted to correct noted problems. For example, on October 1, 1984, the Center upgraded its Adverse Drug Reaction System to include online (immediate response) capability. This upgrade also increased the system's capacity; today, it contains nearly 160,000 reports received from 1980 to 1986. In addition, the system is more timely in terms of its ability to rapidly process and enter data on adverse drug reactions. For example, over a 4-year period (1981-85), due to hardware and procedural changes, the Center reduced the average time for data entry from 730 days to 24 days.

The Center also upgraded the Astro-IV System, resulting in a somewhat more accurate and accessible system for Center reviewers desiring information about new drug applications. According to FDA officials, the agency improved the quality of the data base, which, due to years of neglect, had developed a high error rate. Officials told us that in previous years basic information, such as drug trade names and drug approval dates, was so inaccurate that the system could not even be used for management purposes. Therefore, the improvements were aimed at purging the system of errors in 30 basic data categories, including trade names, active and inactive ingredients, and manufacturers' names.

In addition, the Center improved Astro-IV's accessibility by transferring portions of the data base to Datatrieve, an online software package. The new software allows reviewers to use a terminal to retrieve information on a new drug application simply by entering a numeric code. The

Center also made a concerted effort to encourage greater use of the system by offering reviewers training.

Finally, the Center attempted to improve the timeliness and quality of the New Drug Evaluation/Management Information System by adding a feature that allowed data entry personnel to immediately correct errors. In addition, the Center converted a portion of the system to Oracle, a software data base that allows greater flexibility for data retrieval. And it tried to improve the system by adding a commentary file that allows reviewers and managers to "write" status information into a separate section of the system. The file is designed to provide managers and supervisors with such information as the reasons a drug application is delayed or is not approved. Without the commentary file, managers must obtain this information from manual sources.

Despite these improvements, problems still exist with the systems, as the following sections demonstrate.

Accuracy and Completeness Problems Undermine Adverse Drug Reaction System's Reliability

New software and streamlined procedures helped to reduce the error rate for adverse drug reaction information entered after October 1, 1984, when the new system became operational. However, these changes have had no effect on the larger, older portion of the data base, which includes 97,000 reports entered before October 1, 1984. Our statistically valid sample[9] showed that, in the Adverse Drug Reaction System,

- 36 percent of reports in the system before October 1 contained inaccurate data;
- 14 percent of reports in the system after September 30—when new software was installed—contained inaccurate data; and
- 35 percent of all reports in the system contained inaccurate data.

Our examination of the error types showed that 59 percent of the errors involved a major data element from the adverse drug reaction report—the amount of drug administered to the patient (drug dosage). According to FDA's review procedures, drug dosage information is important in determining the cause of an adverse reaction. This information helps the

[9]The total sample universe in the system was 101,000 reports entered after January 1, 1980. At the time of our test, there were approximately 97,000 reports entered under the old system and 4,000 reports entered under the new system. A system error was identified when an element from the source document was found to be either missing from the computer or entered incorrectly into the system.

reviewer decide if the reaction was caused by an improper and possibly harmful drug dosage.

Our March 1985 completeness test revealed that 26 percent, or more than 26,000 reports received, had not been entered into the system for processing. Both adverse drug reaction reviewers and new drug reviewers were concerned that the system's incompleteness could hinder their ability to use the system to analyze adverse drug reactions and warn the public. For example, if the system showed that a drug was associated with 25 heart attacks, but 100 heart attacks were actually reported to FDA, the reviewer could make an incorrect evaluation. In effect, the new drug reviewer could allow a harmful drug to remain marketed based on incomplete information from the adverse drug reaction system.

On the basis of reviewers' answers to our questionnaire, we also found that 79 percent of all new drug application reviewers did not use the Adverse Drug Reaction System, primarily because they did not feel it was reliable. The Center's Deputy Director for Information Systems told us that FDA required its drug information systems to be 100-percent accurate and complete. Although the 100-percent standard may not be realistic, the error rates demonstrate that the system is significantly inaccurate and incomplete.

Astro-IV System Is Inaccurate and Does Not Support Drug Reviews

While the Center has taken steps to improve the data quality in its scientific system (Astro-IV), the system is still neither completely reliable nor useful to the majority of new drug reviewers. It also falls short of the Center's requirement for 100-percent accuracy and completeness. In testing four major data elements; we found that three—trade name, active ingredient, and manufacturer—had been entered into the system with 100-percent accuracy. The fourth (inactive ingredient) was entered with significant numbers of errors.

Center reviewers said that an important system feature in terms of new drug reviews is the system's ability to search for and list drugs containing specified inactive ingredients. But our accuracy test revealed that

- 17 percent of all new drug applications in the system contained inaccurate data because at least one inactive ingredient was not included;

- 14 percent of all new drug applications in the system contained inaccurate data because two or more inactive ingredients were not included; and
- 12 percent of all new drug applications in the system contained inaccurate data because three or more inactive ingredients were not included.

Thus, if a reviewer used the system to analyze inactive ingredients in a new drug application, a decision on a drug's approvability could be based on faulty information.

Our completeness test revealed that an estimated 99 percent of all new drug applications were included in the system. Because our sampling error was 1.5 percent, we believe the system is essentially complete.

Furthermore, our survey revealed that 89 percent of new drug application reviewers never used Astro-IV because

- the system did not meet their needs,
- data retrieval often required assistance from computer personnel,
- they did not trust the system's reliability, and
- they depended on manual sources of information.

Our survey showed that 78 percent of the Center's reviewers believed that manual sources of information were more important to the new drug application review process than the Astro-IV System or any other automated system. Also, 52 percent of the reviewers believed that the most important source of drug review information was the new drug application itself, which is entirely manual. Medical officers were especially interested in the clinical test data, the portion of the drug application that they must review to assess drug safety and efficacy. In addition, 26 percent believed that outside literature, including such professional texts as the Physician's Desk Reference, was most critical to a new drug application review.

New Drug Evaluation/ Management Information System Is Inadequate for Managers

Although the Center has improved the New Drug Evaluation/Management Information System, the system remains inaccurate. In addition, the Center's mid-level managers stated that because the system is inaccurate, they found it difficult to track and manage new drug application reviews. Specifically, we found that

- 37 percent of the new drug applications listed in the system had been reviewed, but the system continued to show the reviews as pending;

- 6 percent of the new drug applications were shown to be assigned to one reviewer but were actually assigned to another;
- 34 percent of all new drug applications in the system contained one or more errors;
- 18 percent of the new drug application supplements listed in the system had been reviewed, but the system continued to show the reviews as pending;
- 29 percent of the new drug application supplements were shown to be assigned to one reviewer but were actually assigned to another; and
- 51 percent of all new drug application supplements in the system contained one or more errors.

In addition, follow-up discussions with reviewers revealed other problems with the system's data. For example, the system showed that

- pending new drug applications were assigned to three reviewers who had not worked at FDA for 6 months,
- almost 200 applications were assigned to a reviewer who was no longer responsible for those reviews,
- drug review work was assigned to several reviewers who knew nothing about the assignments, and
- a new drug application was assigned to a reviewer who had been deceased for more than a year.

Our completeness test on the New Drug Evaluation/Management Information System showed that 99 percent of the applications had been entered into the system; therefore, with the sampling error of 1.5 percent factored in, we believe the system is essentially complete.

Our survey of the Center's managers revealed that 61 percent used the New Drug Evaluation/Management Information System to track the progress of new drugs under review. Managers and supervisors who used the system told us that such information as drug names, therapeutic uses, and manufacturers of new drugs provided them a good, overall view of division activity. In addition, they said that a feature that allows them to compare the time that a new application has been under review with statutory time frames was important in helping them to manage new drug reviews.

Overall, however, division managers and supervisors expressed dissatisfaction with information in the New Drug Evaluation/Management Information System. They believed that the information was inaccurate and inadequate for assigning work and criticized the system's inability

to provide a drug's intermediate review status. For instance, the system may show that the chemical, pharmacological, and medical reviews are complete, but it does not indicate why the drug is still not approved. While the recently added commentary file allows reviewers to insert status information, this notation is not mandatory and thus does not ensure that the system's intermediate status information is complete.

Finally, managers and supervisors said that it was difficult to keep the system accurate because reviewers were reluctant to spend time updating it. Managers rely on reviewers to provide such updates because reviewers are the best source of new drug application status information. But since the Center considers the management information system to be a management tool and not a scientific tool for reviewers' use, reviewers see little point in keeping the system up to date.

The result is that numerous alternative manual and automated systems exist throughout the Center to assist the reviewing divisions in tracking new drug applications. In one division, the pharmacological section uses a "listing" program on a word processor to track new drug applications. Another division has developed its own management information system for use on a personal computer to better track new drug applications and manage work loads. In addition, many managers and section supervisors use index cards or log books, some of which are detailed and elaborate, to supplement report data in the New Drug Evaluation/Management Information System. Relying on these individual systems rather than on a well-developed and well-maintained automated tracking system inhibits maximum dissemination of drug review status information among the reviewing divisions and, according to Center managers, results in duplicated efforts and wasted time.

FDA Would Benefit From Increased Use of Information Resources Management Concepts

Sound information resources management requires a systematic approach to assessing an organization's information resources management and automatic data processing needs, developing plans to meet these needs, and carrying out the plans to achieve stated objectives. The Paperwork Reduction Act of 1980 and Office of Management and Budget (OMB) Circular A-130 stress that information is a valuable resource and that it must be intensively managed. To that end, the act and OMB guidance require executive agencies to perform their information management activities efficiently, effectively, and economically. Accordingly, the Department of Health and Human Services is responsible for ensuring that component agencies, such as FDA, comply with the act and with OMB guidance. Specifically, under OMB Circular A-130, the Department is required to direct FDA to

- ensure that information systems are complete and accurate;
- conduct strategic planning aimed at acquiring and using information assets to meet program needs;
- make comprehensive requirements analyses, including a survey of user needs and an assessment of required data terminology, before designing information systems;
- ensure that information resources management functions are linked to decision making; and
- improve the operation of regulatory programs through the application of information technology.

Our review of the information activities in FDA's Center for Drugs and Biologics indicates that the Center has made limited progress toward meeting the above requirements. Overall, the Department of Health and Human Services has not ensured that FDA is adequately managing its information resources.

FDA Did Not Provide the Senior Information Resources Management Official With Adequate Support

The Paperwork Reduction Act of 1980 directed each agency head to appoint a high-ranking official to ensure that the agency effectively managed its information resources. Accordingly, the Secretary of Health and Human Services designated the Assistant Secretary of Management and Budget as the senior departmental official responsible for overseeing activities administered under the Paperwork Reduction Act. In addition, FDA appointed the Associate Commissioner for Management and Operations as the designated information resources management official. Despite the appointments of these two senior managers, many of FDA's information management difficulties continue.

From 1981 (when the Paperwork Reduction Act was first implemented) until 1985, FDA's top management did not provide strong organizational support for information resources management. During that time, according to agency officials, FDA's Associate Commissioner for Management and Operations was the designated senior information resources management official. This individual's normal full-time duties were considerable, for they encompassed managing the day-to-day operations of the entire agency. Recognizing the importance of this position to ensure "that FDA activities are conducted in accordance with sound management practices, and adhere to applicable laws and regulations," FDA provided substantial organizational support. For example, the Associate Commissioner for Management and Operations is supported by a deputy, the director of the Parklawn Computer Center in Rockville, Maryland, and five division directors who manage such areas as finance, personnel, and contracts. Each of these managers, in turn, is provided organizational support at the division level. However, FDA did not provide the Associate Commissioner for Management and Operations the organizational support required of and commensurate with his information resources management responsibilities.

On August 2, 1985, acting on a task force report on FDA operations that recommended establishing an agencywide information management function, the FDA Commissioner approved the establishment of a Division of Information Resources Management and appointed a permanent director to oversee the new division. In addition, the Commissioner transferred responsibility for automatic data processing planning, budgeting, systems management, and telecommunications to the new director and ordered that organizational changes be made to support this new division. Like his predecessor, the newly appointed official will be responsible for major tasks other than information resources management. For example, he will continue to serve as the director of the Parklawn Computer Center, which has over 100 employees and does computer work for other federal agencies as well as FDA.

The following sections demonstrate the need for a senior information resources management official who, to ensure that FDA's information resources are properly identified and managed, receives adequate organizational support from the agency.

Inadequate Quality-Control Procedures Contributed to Unreliable Systems

OMB Circular A-130 requires agencies to ensure that information systems are accurate and complete. However, as discussed in chapter 2, our tests revealed that FDA's three main drug information systems are inaccurate, and one is incomplete. These reliability problems continue because

- quality controls over the data in the Astro-IV and Adverse Drug Reaction systems were only recently established, and FDA officials told us that they had decided not to attempt to correct all data base errors, but to concentrate on new data entries instead;
- controls over the receipt and processing of adverse drug reaction reports were insufficient, resulting in an incomplete system; and
- reviewers were reluctant to keep the New Drug Evaluation/Management Information System up to date because they did not believe the system met their needs.

FDA officials told us that the data errors in both the Astro-IV and Adverse Drug Reaction systems had increased during the years when no quality-assurance procedures were in effect. When management decided to upgrade both of these systems in the late 1970s, improving data quality took top priority, and edit procedures were established. According to agency officials, these improvements have increased the accuracy of data entry and have made the systems more reliable. FDA management also noted that despite such new internal controls as online edits and quality checks, much of the older portions of the data bases remains seriously in error.

In addition, due to inadequate controls over the receipt and input of adverse drug reaction information, 26 percent of reports received are not being processed. In our 1982 report (mentioned on page 15), we questioned the agency's procedures because there were too many intermediate steps, resulting in lost reports. Consequently, the Center changed its process and required that all reports be sent directly from the appropriate drug review division to the Reports Evaluation Branch, where they are coded and entered into the computer. This procedure resulted in some improvement in data base completeness; however, many reports are still not being forwarded for processing. The Center's drug review division staff either does not know or is not following established procedures for the transfer of adverse drug reaction reports to the branch. Consequently, FDA is implementing a regulatory change that requires companies to forward all adverse drug reports directly to the Center's Reports Evaluation Branch, where they will be processed and then sent to the reviewing division. We believe that this change,

over time, could make the adverse drug reaction data base more complete.

Finally, we found that the New Drug Evaluation/Management Information System was inaccurate because reviewers did not keep it updated and because no standardized quality-control procedures existed for the timely entry of new data and revisions of old data. Center top-level managers use this system to monitor the progress of new drug applications through the approval process. However, one FDA study reported that, "No criteria have been established regarding management's expectations toward the accuracy of data entry," and noted that the drug review divisions' timeliness in entering information varied substantially. This study concluded, "Without knowing the extent of certainty that data will be entered, less reliance can be associated with the system by potential users."

Two acting division directors indicated that they were reluctant to devote such scarce resources as clerks and consumer safety officers to updating the management system since the system did not fully meet their needs and since they considered maintenance of the system's data base a low priority. Because Center management has not insisted on standard procedures for management information system updates, each division performs this task differently. The result is that the quality of the system's data varies widely, depending on the division doing the updates, and, overall, as shown in chapter 2, is inadequate.

Long-Range Information Resources Plan Has Not Been Developed

FDA has not developed adequate long-range planning documentation for information resources. OMB Circular A-130 requires that agencies develop a comprehensive information resources management plan to ensure that information requirements are adequately met, to prevent duplication, and to promote the efficient and effective sharing of resources. The circular also requires agencies to establish multi-year strategic planning processes for acquiring and operating information technology that meets program and mission needs.

Officials of the Office of Management Systems and Policy, which falls under the Associate Commissioner for Management and Operations, told us that FDA had not prepared a comprehensive long-range information plan since 1977. They also explained that FDA did not have a formal planning process and that most agency planning occurred in individual program offices without review or coordination by the agency's planning and policy office. In addition, a planning official said he did not

believe a formal automatic data processing plan was necessary since data processing planning information was included annually in the budget justification process. Officials from two FDA offices—Planning and Evaluation and Management Systems and Policy—told us that they saw little value in preparing formal automatic data processing plans primarily because their data processing budget submissions were routinely changed by OMB and the Department of Health and Human Services.

According to Center officials, planning is carried out for individual systems and varies for each system. The Center also prepares a functional description of planned major system development projects. The Division of Information Systems Design prepares a status update for each system under development, generally stating the current fiscal year's accomplishments and describing the Center's plan for the next fiscal year. If development is expected to take a year or less, planning is more informal, but milestones are specified.

Requirements Analyses Were Not Adequately Conducted, and Attempts at Standard Drug Terminology Have Not Been Successful

The Federal Information Resources Management Regulation and OMB Circular A-130 state that agencies must adequately document the purpose that an information system is intended to serve. At a minimum, a requirements analysis should include a survey of user needs. In addition, to enhance the compatibility of systems within the agency, the analysis should include an assessment of the standard data terminology that the system will need. However, the Center's reviewers have not participated in the planning, development, or subsequent modification of such information systems as Astro-IV and Adverse Drug Reaction. In addition, despite several limited efforts, the Center has not standardized drug terminology for effective use throughout its systems.

FDA Has Not Adequately Considered Reviewers' Needs in Developing Drug Systems

FDA has not adequately considered reviewers' needs in developing and implementing its systems. Federal regulations concerning automatic data processing systems require that comprehensive need determinations be made before a computer system is acquired or replaced. For example, Federal Information Resources Management Regulation, Section 201-20.003, states:

> "The acquisition of an initial information resource capability or the augmentation or replacement of an existing capability shall be preceded by a comprehensive requirements analysis that is commensurate with the scope and complexity of the program objectives and mission needs."

In our May 1980 report (see page 14), we said that user needs received little consideration when FDA's drug information systems were being developed. These systems were designed and put in place during the late 1960s and early 1970s and have been modified and improved periodically. However, detailed requirements statements and justification data for both Astro-IV and the Adverse Drug Reaction System have not been prepared to relate the systems or their modifications to the Center's primary mission of ensuring the safety and efficacy of drugs.

Center officials assured us that these systems met the reviewers' scientific needs; however, we found that 89 percent of the Center's reviewers did not use Astro-IV, and 79 percent did not use the Adverse Drug Reaction System. For example, Center officials said Astro-IV was useful to the scientific analysis of new drug applications, when, in fact, according to official usage reports, only a few reviewers ever requested information from the system. During a 16-month period (December 1983-April 1985), only 10 of 214 requests for information from the system were from reviewers. Also during this period, total requests for information from the system averaged slightly more than three requests per week.

A senior information resources management official should ensure that (1) user needs are adequately considered before system implementation and (2) inadequate systems are appropriately enhanced, or replaced, or scrapped. In doing so, FDA can capitalize on existing information technology critically needed to more effectively approve and monitor drugs.

Standard Terms Are Not Used in Systems

FDA officials told us that, over the past several years, the Center conducted studies and made several attempts to standardize its drug terminology. Although it has achieved some limited success, the Center has not successfully incorporated standard drug terminology into its systems, largely because management has not decided on the terminology to be used.

OMB guidance on information resources management states that a lack of compatibility among systems has emerged as a significant problem. OMB further states that agencies often acquire technology that is incapable of communicating with other agency systems in a manner that enhances compatibility. To avoid these problems and to facilitate compatibility, OMB guidelines state that an agency must adequately assess and decide on the type of standard data terminology the system will need.

FDA officials stated that standardization of drug data elements should be a first step toward system integration because it would enable the different automated systems to share data and would allow reviewers to obtain all available information on specific searches when the data are cross-referenced from one system to another. Standardization and cross-referencing of drug data elements could also ultimately reduce work load and improve quality control by eliminating redundant data entry in such systems as Astro-IV and the New Drug Evaluation/Management Information System.

An FDA committee has studied the standardization issue since 1981. A committee member told us they had identified several options for standardizing drug terminology and had recommended that the Center develop uniform drug terminology for its various automated systems. During the same time that the FDA committee was studying this issue, four successive lexicographers developed tables and a dictionary for standardized use within the Center's systems. However, FDA management did not ensure that any of the recommendations were implemented or that the tables and dictionary were fully incorporated into the Center's systems. Thus, FDA still lacks standard drug terminology.

The Center had limited success in two standardization areas. First, according to Center officials, it standardized some drug ingredient terminology used in the Astro-IV System. Officials told us that this retrieval feature benefited only a few people who were very familiar with the system. Second, the Center incorporated into the Adverse Drug Reaction System a feature that promotes standardized terms limited to that system. The system compares new data input with information already in the system. If the terms do not match, the system alerts the data entry person to check the entry for proper terminology.

Because the Center has not effectively incorporated standard drug terminology among its automated systems, the users cannot easily retrieve similar data from the different systems. Thus, valuable time is lost in trying to identify the exact term to use to access complete information from each of the systems. For example, to retrieve new drug application information, the New Drug Evaluation/Management Information System requires the term "new drug application and a 5-digit number," while the Astro-IV System requires the term "N and a 5-digit number." A user must use the exact term when retrieving information from these systems. Most reviewers and managers we interviewed agreed on the need

for standard drug terminology. Center officials said that there were various ways to standardize and that, although each option had its advantages and disadvantages, standardization outweighed the disadvantages of any one option.

Drug Information Systems Do Not Support Informed Decision Making

Neither Astro-IV nor the Adverse Drug Reaction System is adequately linked to the drug review process. The Astro-IV System does not help most reviewers make informed decisions on the safety and efficacy of new drugs. In addition, the Adverse Drug Reaction System does not adequately support decision making in monitoring adverse reactions because management has not decided how to use the system's information. An important requirement of OMB Circular A-130 is that information resources management functions be linked to program management, which in FDA's case is linked to regulatory decision making. This provision mandates that a regulatory agency's information systems support the ability of agency personnel to make informed policy decisions.

Astro-IV Does Not Support Drug Reviewers

Our interviews revealed that most reviewers did not rely on any automated system, including Astro-IV (considered by Center officials as the scientific system) to review the safety and efficacy of new drugs. Of the 62 reviewers interviewed, only 7 said they used Astro-IV. Many reviewers acknowledged that the information in the system might be useful, but overall it did not adequately support decision making in the drug review process. Several reviewers noted that they needed a system that would allow them to manipulate the new drug application data on-line and to review adverse drug reactions on-line.

To perform their analyses, new drug reviewers rely primarily on paper and manual procedures; they rely on the new drug application itself supplemented with outside literature. Thus, most new drugs are reviewed and approved without the use of any of the Center's computer systems.

Efforts by Center computer personnel to increase Astro-IV usage have not been successful, largely because the system does not meet reviewers' needs. One senior FDA official noted that information services personnel were constantly trying to "sell" Astro-IV to new drug application reviewers—usually with little success. This official also stated that because reviewers did not use Astro-IV, the system "should have been dumped ten years ago," but continued to exist because of bureaucratic inertia and management's indifference.

Management Has Not Clarified the Use of Adverse Drug Reaction Information

A different situation was evident concerning the Adverse Drug Reaction System, which on October 1, 1984, was upgraded to an online capability. Although the Center has succeeded in improving the system's technical aspects, it has not decided how reviewers should use the system's information to make informed decisions on drug safety. Reviewers in the drug review divisions are responsible for assessing the safety of drugs both before and after they are approved for marketing; however, they have little direct access to the Adverse Drug Reaction System. Thus, these reviewers must rely on their memory or any personal notes to determine whether the number of incoming adverse drug reactions warrants corrective action. Conversely, adverse drug reaction reviewers in the Reports Evaluation Branch, who do not have the authority to approve drugs or make labeling changes, have direct terminal access to the Adverse Drug Reaction System. We are concerned that a lack of interaction between these two reviewing groups could hinder the Center's ability to inform the public of adverse drug reactions.

An FDA study on the role of the adverse drug reaction program in the Center's overall scheme of drug regulation expressed similar concerns on the apparent lack of communication between the different reviewing groups. Some key findings follow:

- Reviewers in the drug reviewing divisions felt compelled to keep separate files on adverse drug reactions because they were afraid of not having any information.
- Adverse drug reaction reviewers in the Reports Evaluation Branch felt like "drones" who spent much time entering data and were prevented from analyzing data or developing findings.
- Individual medical officers and adverse drug reaction program managers maintained separate, but incomplete adverse drug reaction monitoring systems.

The study recommended that management "sort out the Reports Evaluation Branch's role vis a vis the drug reviewing divisions in order to clarify its priorities, and to allow its resources to be used efficiently and effectively." In addition, a Reports Evaluation Branch official told us that coordination between the branch and the drug review divisions was not adequate because the two groups did not interact very often. This official noted that because drug reviewers (especially medical officers) were "autonomous," few were willing to communicate with the adverse drug reaction reviewers.

Our discussions with adverse drug reaction reviewers in the Reports Evaluation Branch and personnel in the drug reviewing divisions revealed continuing confusion over responsibility for the collection, analysis, and communication of adverse drug reaction information. Currently, both the Reports Evaluation Branch and the reviewing divisions have some responsibility for monitoring adverse drug reactions. According to branch officials, the adverse drug reaction reviewers function as the first-line interpreters of the 40,000-plus reports received annually. They receive copies of adverse drug reactions sent to the Center and have immediate access to the automated data in the Adverse Drug Reaction System. These reviewers analyze the data to determine whether reported reactions are occurring at a rate significant enough to warrant further research. Because the branch lacks the authority to approve labeling changes or drug recalls, its role is strictly confined to information analysis.

Under current procedures, the branch only provides information on adverse reactions to the new drug application reviewing divisions. Each of the drug review divisions has regulatory authority to approve labeling changes or to withdraw approval for a marketed drug. Ordinarily, a medical officer involved in reviewing similar classes of drugs will monitor the adverse drug reactions as they arrive in the division document room. Because most of these new drug reviewers do not have direct access to the automated system, they are limited to either (1) requesting adverse drug reaction data from the branch or (2) manually reviewing the adverse drug reactions as they are periodically filed with the new drug applications. However, 16 of the 24 medical reviewers we interviewed told us they never used reports from the Adverse Drug Reaction System. One reviewer said he did not use the system because it did not contain such information as the number of prescriptions filled in pharmacies. Another medical officer stated that he did not think the system was complete; therefore, he used the manual records in the new drug application files.

To improve the internal communication of adverse drug reaction information, the Director, Office of Epidemiology and Biostatistics, established an informal liaison between the two reviewing groups. In addition, the Director encouraged the scheduling of joint safety conferences between adverse drug reaction reviewers and division reviewers who handle similar classes of drugs. At these conferences, reviewers should discuss the identified reactions, their statistical significance in the population, and the possible regulatory actions that can be taken. Agency officials stated that if a health risk were possible, the Center

would issue a memorandum notifying other FDA reviewers, the pharmaceutical company, pharmacists, hospitals, and other concerned parties.

Overall, the attempts to improve communication of adverse drug reaction information have had limited success. One reviewer noted that since the Zomax hearings, discussions between the Reports Evaluation Branch and the drug reviewing divisions had increased. Several drug reviewers stated that they now meet informally with their adverse drug reaction counterparts to discuss safety issues. However, our interviews also revealed continuing disagreement over the regulatory role of adverse drug reaction reviewers and the Adverse Drug Reaction System, especially from division managers. One division director stated that:

"Adverse drug reaction reports from the REB [Reports Evaluation Branch] are useless. The reviewers in the division look at their own hardcopies and have never been forewarned of problems by the [branch]."

Another director remarked that only 1 of his medical officers (of 10 assigned) communicated with the adverse drug reaction group. In addition, a reviewer in one division said that he must justify to the division director his reasons for contacting adverse drug reaction reviewers; therefore, there was very little interaction. In our opinion, the Center's communication problems are caused by FDA's inability to clarify and establish a viable regulatory role for the adverse drug reaction reporting program. We believe that these continuing problems in FDA's management of adverse drug reaction information could hinder the agency's ability to inform the public of possible drug hazards.

FDA Is Attempting to Use Up-To-Date Technology to Reduce Paper Burden

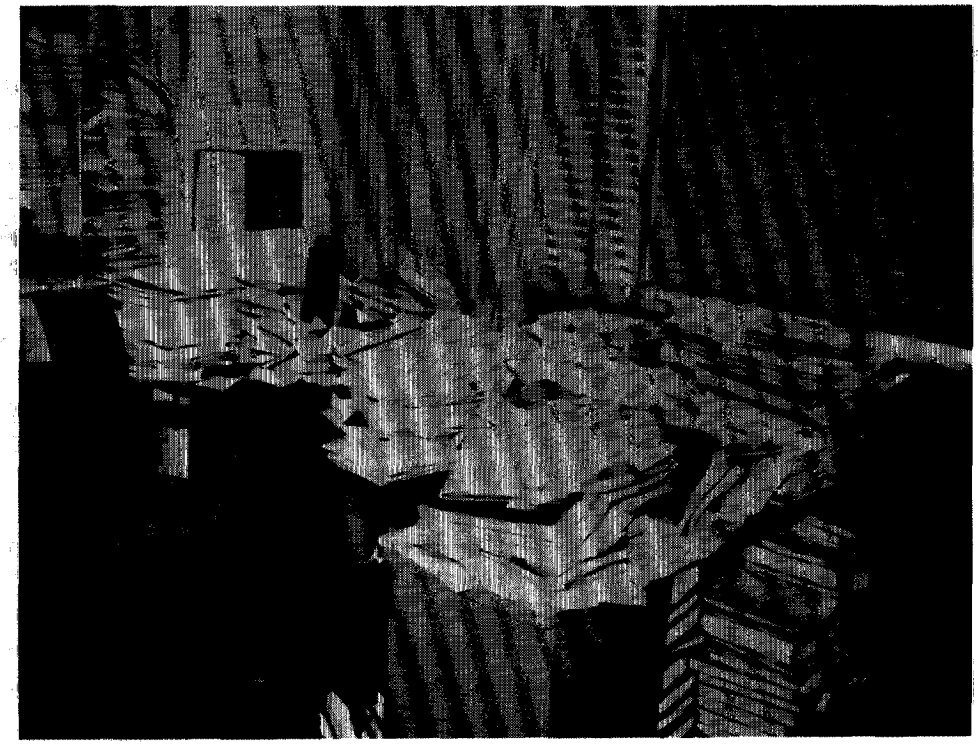
OMB guidelines require agencies to improve the efficiency and effectiveness of regulatory programs through the application of information technology. To that end, FDA and the Center have studied the possible impact of introducing newer technology on drug regulation. In particular, the agency is exploring means to ease the storage and handling of large amounts of documentation. Options being studied include electronic data transmission, laser disk scanners, bar coding, and microfiche. Not having effective, up-to-date automated systems has contributed to the Center's need to use voluminous amounts of documents in its drug regulatory process.

Paper Load Hinders Drug Regulation

According to an FDA study, paper flowing into the Center totaled more than 1.2 million pages in 1983 (latest available information) for original new drug applications alone. Since 1962, when companies were required to demonstrate that a drug was both safe and effective, the total amount of paper has increased each year. As a result, division document rooms—and some reviewers' offices—are overloaded with volumes of paper, and severe handling and storage problems have been created. In one case, according to a Center manager, a new drug application was inadvertently hidden beneath other recently delivered applications, resulting in a 4-month delay before it was given to a reviewer.

As the photograph in figure 3.1 demonstrates, the paper-load problems facing the Center's new drug review divisions are serious and require the attention of FDA's information resources management official. The reviewer (who is also a division director whose office is depicted) stated that his division area was so cluttered with paper, boxes, and volumes that "it looked like a junk heap" and "was on the brink of catastrophe." Our observations in over 120 reviewers' offices and 9 document control rooms confirmed this situation. In our opinion, the large volume of paper and the lack of space act as a detriment to efficient and effective drug review.

Figure 3.1: Paper Load in a Manager/ Reviewer's Office



FDA Is Exploring Other Technologies

To resolve its paper-load problems and to prevent future difficulties with document handling, FDA is exploring several possible applications of information technology, as described below.

Electronic Transmission

The Cardio-Renal Division, one of FDA's new drug application reviewing divisions, is studying the feasibility of using electronic transmission through pilot projects involving two companies. A research company and a drug company have devised an experiment that will allow FDA to compare the effectiveness of manual drug reviews with electronic drug reviews. The first phase of the experiment began in May 1985 when the drug company forwarded two new drug applications to the Cardio-Renal Division, and a reviewer was assigned to each drug. The two reviewers completed their evaluations in January 1986.

During the second phase of the experiment, in April 1986, the drug company electronically submitted both drug applications to FDA, using the research company as the intermediary. The research company provided all the necessary equipment and devised the software for use in electronic drug reviews. The same reviewers were also involved in the

second phase, but they switched and reviewed each other's drugs, using the electronic means. After the projects are completed in September 1986, the Director of the Office of Drug Research and Review will assess the online submission's effectiveness in reducing paper within the new drug application reviewing divisions and in improving the quality of the review.

Laser Disk Scanners

In August 1984 the FDA Commissioner established an agency task force to assist in his transition into the agency. On September 4, 1984, the task force issued to the Commissioner a report entitled Management of Information. The Commissioner then directed the Director of the Office of Management for the Center for Food Safety and Applied Nutrition to implement some of the report's recommendations.

One of the task force's conclusions was that FDA needed to improve its ability to store and retrieve information. The task force noted that FDA was continually acquiring data in vast amounts and needed to utilize technologies that would allow people faster and more precise access to the data. One such technology is the optical laser disk, where data are stored and later retrieved with a laser. Thus, pending the receipt of budget allocations, FDA is procuring an optical storage and retrieval system that will be placed in four areas: the Center for Food Safety and Applied Nutrition, the Center for Devices and Radiological Health, the Center for Veterinary Medicine, and the adverse drug reaction reporting group within the Center for Drugs and Biologics. The task force believes the adverse drug reaction group is the best area for experimenting with this technology, since it already uses automatic data processing systems for analyzing data.

Bar Coding of Documents

Another technology under consideration is bar coding. Most bar coding technology centers around the use of a stamped code read by light sensors, similar to the devices used in department and grocery stores.

FDA officials said this type of tracking technology could help prevent loss of documentation and reduce data entry errors. For example, with a bar code, clerks in the Center's main document room will be able to immediately assign identification numbers and other applicable data, such as the drug name and manufacturer, to new drug applications and thereby help to prevent lost documents. As the application is sent from one work station to another during the approval process, use of the bar

code will reduce the number of required redundant data entries and consequently help reduce data entry errors.

Microfiche

Since 1977, the Center has participated in experiments having potential for decreasing the amount of paper in the new drug applications reviewing divisions. One such experiment was the use of microfiche, instead of paper or hard copy, for certain portions of a new drug application. The experiment revealed that the microfiche greatly decreased the volume of paper. For example, a pharmaceutical company prepared approximately 200,000 pages of hard copy for a new drug application. The company estimated that this application required 115 linear feet for storage in the company filing area. The equivalent in microfiche required 4.5 linear feet. A Center microfiche review group acknowledged that microfiche was a viable medium for presenting certain portions of applications to reviewers.

Although companies were willing to submit portions of new drug applications on microfiche, several reviewers complained of eye strain when using the microfiche; others objected to it because they wanted to write their notes directly on a hard copy for easy referral. A few reviewers have accepted microfiche submissions, but most prefer, and so request, a hard copy of the new drug applications.

Conclusions, Recommendations, and Agency Comments and Our Evaluation

Conclusions

FDA's automated drug information systems do not adequately assist Center officials in approving new drugs needed to treat critical illnesses and in identifying hazardous drugs that should be withdrawn from the marketplace to prevent adverse drug reactions and sometimes death.

FDA does not have complete, accurate, and up-to-date information systems critically needed to assist it in (1) reviewing and approving new drugs and (2) monitoring adverse drug reactions. Furthermore, the information systems it has do not meet reviewers' needs and are not readily accessible to personnel directly involved with approving new drugs or warning against hazardous drugs. FDA has a history of inaccurate and incomplete drug information systems that do not adequately meet users' needs. Although FDA has made some improvements, this situation continues to exist today for the systems associated with approving and monitoring new drugs.

Until FDA holds a senior official and program managers accountable for proper information resources management, as provided for in the Paperwork Reduction Act and OMB guidance, it will not be able to effectively use automation in meeting its responsibilities. Proper information resources management, which is not being achieved at FDA, includes (1) ensuring that systems are complete and accurate, (2) planning for long-range needs, (3) ensuring that systems are properly linked to an agency's decision-making process and meet users' needs, and (4) appropriately using applicable information technology.

FDA needs to set a top priority on obtaining accurate, complete, and effective automated information systems. As part of this effort, it needs to provide the senior official adequate organizational support to ensure that information resources are properly managed.

Recommendations

Considering the potential risk if information systems do not properly assist FDA in identifying hazardous drugs and in expeditiously approving new drugs needed to treat illnesses, the Secretary of Health and Human Services should improve the management of FDA's information resources in keeping with the requirements of the Paperwork Reduction Act. We recommend that the Secretary, through the Assistant Secretary of Management and Budget, direct the FDA Commissioner to take the following actions:

- Develop and implement precise instructions for the receipt, processing, and input of adverse drug reaction reports, particularly in the area of document control, to ensure that reports are entered into the system.
- Develop and implement specific criteria for the timely entry of new drug application status and assignment information into the New Drug Evaluation/Management Information System.
- Evaluate the Astro-IV System to determine its role in FDA. Specifically, assess whether it is to be used in the drug review process or as an administrative tool supporting other programs. Only if the agency decides to use the system for drug reviews should it correct the system inaccuracies identified in this report. The agency should cease spending resources to upgrade the system's accessibility and utility for drug reviewers until this evaluation is completed.
- Monitor the reliability of data in all three systems by periodically testing data input procedures and system output.
- Implement standard drug terminology to enhance the integration of drug information systems.
- Identify and document reviewers' and managers' automation needs through a rational assessment and development process and develop systems that directly support the review and analysis of drug applications and the monitoring of approved drugs. As part of the assessment and development process, (1) evaluate the existing systems and determine if it would be more cost beneficial to enhance, replace, or scrap them and (2) evaluate the use of up-to-date technology to enhance data base integrity and to solve paper-volume, handling, and storage problems.
- Prepare long-range automatic data processing plans to assist (1) in identifying the automated technology and information systems the Center needs to carry out its mission and in (2) justifying resulting budget requests.

Agency Comments and Our Evaluation

We requested written comments on a draft of this report from the Department of Health and Human Services. Although the Department generally disagreed with our findings, it concurred with all but one of our recommendations. Generally, the Department was concerned that certain agency documents and statements may have contributed to what it believes is an incorrect perception that specific information systems were intended to support the drug review process. In particular, the Department cited GAO's treatment of the Astro-IV System as its primary concern, a system that it maintains was not intended to support new drug reviewers. We disagree; the evidence we obtained from FDA officials and documents strongly supports our assessment of the purpose of FDA's

drug information systems. However, in light of FDA's apparent confusion over the intended use of the Astro-IV System, we have changed our recommendation from requiring the agency to correct system errors to recommending that FDA perform a complete assessment of Astro-IV to determine its actual role in agency operations.

FDA's comments and our detailed evaluation of those comments are presented in appendix III.

Request Letter

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OF THE
COMMITTEE ON GOVERNMENT OPERATIONS
RAYBURN HOUSE OFFICE BUILDING, ROOM B-372
WASHINGTON, D.C. 20515
(202) 225-2548

March 28, 1984

The Honorable Charles A. Bowsher
Comptroller General of the United States
General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Bowsher:

The principal function of the Food and Drug Administration is to collect and analyze information on the safety and effectiveness of a wide range of consumer products. Recent oversight hearings have disclosed that FDA needs to improve the way it manages and uses information. Information management deficiencies weaken FDA's regulatory programs, create unnecessary backlogs, cause inefficient use of resources, and, in some instances, result in uninformed or misinformed decisionmaking. I believe FDA must improve its information management policies and procedures if it is to protect the public from unsafe foods, drugs, devices, and cosmetics.

Accordingly, the subcommittee requests that the General Accounting Office undertake a comprehensive review of the manner in which FDA collects, processes, uses, and disposes of information. The subcommittee staff has already discussed this matter with your Information Management and Technology Division.

The study should review FDA's information management practices and procedures. At a minimum, it should assess the information management capacity of the National Center for Drugs and Biologics, which, in carrying out its responsibility for insuring the safety and efficacy of new drugs, receives an exceptionally high volume of scientific data.

The Honorable Charles A. Bowsher
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The review should look at both manual and automated systems, keeping in mind such questions as:

** Are manual systems efficiently managed and controlled to facilitate such activities as new drug approvals?

** Should other types of information technology be used to facilitate handling and storage problems?

** Are FDA professionals aware of and using existing ADP systems?

** Could additional automation efficiently reduce paperwork?

** Are existing systems complete and accurate?

** Are user needs adequately considered during system development?

In your final report to the subcommittee, I would appreciate your assessment of how FDA can better manage information to effectively and efficiently carry out its programs. Also, I would appreciate receiving any legislative recommendations which you believe would help FDA in this effort.

I look forward to your report on this subject.

Sincerely,

Ted Weiss

TED WEISS
Chairman

Results of the Statistical Accuracy and Completeness Tests of the Center's Automated Systems

On the basis of the data we analyzed, the information below presents the estimates and their associated sampling errors at the 95-percent confidence level.

Figures in Percent

Completeness Tests	Estimated to be complete	Sampling error
Adverse Drug Reaction System	73.9	4.80
Astro-IV	99.0	1.99
New Drug Evaluation/Management Information System	99.0	1.54

Accuracy Tests	Estimated to be inaccurate	Sampling error
Adverse Drug Reaction System		
Data base prior to October 1, 1984	36.0	6.0
Data base after installation of new software on October 1, 1984	14.0	7.0
Total data base	35.0	7.0
Astro-IV		
One or more missing ingredients	16.5	4.2
Two or more missing ingredients	13.8	3.8
Three or more missing ingredients	11.9	3.6
New Drug Evaluation/Management Information System		
New drug applications		
Shown pending but actually completed	37.4	19.7
Percent actually assigned to someone else	6.0	5.0
Percent lines in error	34.0	16.0
New drug application supplements		
Shown pending but actually completed	18.2	10.9
Percent actually assigned to someone else	28.8	20.4
Percent lines in error	50.9	30.4

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

JUL 18 1986

Mr. Richard L. Fogel
Director, Human Resources
Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Fogel:

The Secretary asked that I respond to your request for the Department's comments on your draft report, "Drug Regulation: FDA's Computer Systems Need To Be Better Managed." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT, "DRUG REGULATION: FDA'S COMPUTER SYSTEMS NEED TO BE BETTER MANAGED" REPORT NO. IMTEC-86- DATED MAY 1986

General Comments

We appreciate the opportunity to comment on the draft report. We have a number of concerns about the text of the report and would like to clarify the premises upon which it is based.

We believe it is important for GAO to understand that, while the original intent and certain subsequent documents and statements may have contributed to the perception that the systems were meant to provide fundamental support to the new drug review process, the evolutionary development and current use of the systems is not now as the report suggests. FDA has taken steps to correct the record about the primary function of the various computer systems. Even more importantly, however, unsafe and ineffective drugs could never be approved as a consequence of inadequacies in these systems as stated in the report.

See comment 1.

1. The Astro-IV system, while occasionally searched by reviewing chemists, is primarily used to support product substitution programs at the state level, to support the Maximum Allowable Cost program under Medicaid for the Health Care Financing Administration, and to support FDA's reporting requirements under the Freedom of Information Act and the Drug Price Competition and Patent Restoration Act.

   From a review of the data elements in the Astro-IV system and a thorough understanding of the new drug evaluation process, it can be seen that the Astro-IV system is intended to be of very limited use to reviewers. Decisions on new drug applications are made on the merits of the data contained in the applications. In FDA's opinion, the inaccuracies cited by GAO are not important enough to warrant the expenditure of resources that would be required to improve the completeness and accuracy of the excipients file because that part of the Astro-IV data base - the only part found by GAO to have inaccuracies - is seldom used. The need for continuing to maintain this data will be reevaluated.

See comment 2.

See comment 3.

   The report's statement that, "...if a reviewer used only the system to analyze inactive ingredients in a new drug application, a decision on a drug's approvability could be based on faulty information," is misleading. The most important source of drug review information - including inactive ingredients information - comes from the new drug

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application and from printed material - such as scientific journals, publications, and books. No reviewer would rely solely on the Astro-IV data base for information about inactive ingredients, primarily because the most complete computer system possible could only briefly summarize the vast amount of information known about inactive ingredients.

See comment 4.

2. The report does not acknowledge that FDA made a policy decision in 1983 that the primary adverse drug reaction review would be done by the Division of Epidemiology and Surveillance (DES) in the Office of Epidemiology and Biostatistics. DES reviewers communicate their information to the approving divisions through safety conferences, which were initiated shortly after GAO began its audit. These safety conferences are working remarkably well, particularly in the last 6 months

See comment 4.

The principal role of the medical reviewers in the approving divisions is to approve drug applications. The reviewers' job in the Division of Epidemiology and Surveillance is to do postmarketing surveillance based on Adverse Drug Reactions (ADRs) to make an initial assessment and to communicate findings to approving divisions. A major goal of separating postmarketing surveillance from the review division is to lessen the burden on these divisions so that they can concentrate more fully on the timely review of new drug applications.

See comment 5.

ADR data are distinct from clinical trial data and require a different type of initial evaluation than is given to clinical trial information presented in the new drug application. The skills involved in the initial review of ADRs (observational, epidemiologic analysis not experimental clinical trials analysis) are markedly different than those involved in reviewing a new drug application. We believe such initial evaluations should be done by appropriately trained individuals whose primary responsibility is postmarketing surveillance.

See comment 4.

Therefore, the report is inaccurate in stating that management has not decided how to use the system's information and in stating that management has not clarified the use of ADR information. FDA has a firm understanding of how ADR data should be used and mechanisms for doing this are in place.

3. GAO's conclusion that ADR system data are inaccurate and incomplete is based on outdated information.

See comment 6.

While it is true that the ADR system is missing data prior to 1980, a major decision was made not to go back and attempt to correct past inaccuracies. Instead efforts have been concentrated on the accurate transcription and entry of current reports. GAO was fully informed of this at the outset

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See comment 6.

of its audit work regarding the ADR system. GAO was also informed that the entire ADR system was about to change; with new regulations, new reporting requirements and new systems to begin on August 23, 1985. The changes were accomplished. Therefore any findings or conclusions drawn from the system and data prior to that time were out-dated before the audit was completed, and have limited, if any, applicability for the new system.

See comment 7.

As to inaccuracies in the ADR system, it is significant that the report recognizes that the inaccuracy rate in the ADR data had dropped from 35% to 14% at the time of the review. This is an important gain that reflects the success - even at an early date - of the changes to the system that FDA implemented.

See comment 8.

It should be noted, however, that the report incorrectly states that FDA requires 100% accuracy for its information systems. Since the ADR data received by FDA from the source is often handwritten and inaccurate, it would be impossible to ever achieve 100% accuracy. Further, the report does not define the term "inaccuracy" as it is used in reference to either the ADR system, or to categorize the significance of various types of errors. Inaccuracies may involve dose and certain other information that may not be important. In FDA's opinion, the key accuracy data involves

a. the year in which the event occurred
b. the name of the drug
c. a description of the reaction.

We estimate the current error rate for these critical data elements to be less than 1%.

4. The report incorrectly suggests that both HHS and FDA management have failed to adequately support ADP development and use in the Center for Drugs and Biologics.

See comment 9.

FDA's philosophy has been that the organizational units closest to the function needing ADP support are in the best position to develop and implement systems to meet those needs. We still believe this to be true. This does not mean, however, that HHS management - and FDA top management in particular - have maintained a hands-off posture with regard to ADP support. FDA has provided funding, equipment, and systems design support to the maximum extent possible given

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the agency's limited resources. Furthermore, the Commissioner of Food and Drugs has established information resources management as one of his ten highest priority action plan items. He has, further, established a Director of Information Resources Management (IRM) with a staff devoted to identifying and fulfilling agency ADP needs. The Director, who also manages the Parklawn Computer Center, spends the majority of his time working with the Centers on IRM matters, as well. The Commissioner has also provided specific support and personal encouragement for revising and modernizing the Adverse Reaction Reporting system to better meet the drug regulatory needs of the Agency. Finally, the Commissioner asked the Associate Commissioner for Management and Operations to personally spend half his time to assist the Center with a variety of management needs, one of which is revising the New Drug Evaluation/Management Information System (NDE/MIS). The Associate Commissioner, along with two of his division directors and their staffs - (the Director of the Division of Management Systems and Policy and the Director of the Division of Information Resources Management) have devoted a considerable amount of time and effort to helping the Center revise the NDE/MIS to meet the needs of management for current, complete, and accurate information regarding the flow of new drug applications through the review process. These efforts are beginning to bear fruit, as the changes are implemented. GAO was fully informed about those initiatives that had begun during the time its audit was in process.

See comment 9.

GAO Recommendation

We recommend that the Secretary direct the FDA Commissioner to comply with the Paperwork Reduction Act of 1980 by initiating the following actions:

1. --Develop and implement precise instructions for the receipt, processing, and input of adverse drug reaction reports, particularly in the area of document control, to insure that reports are entered into the system.

Department Comment

We agree. FDA had already identified these weaknesses in the ADR system and initiated corrective action prior to the GAO review. Instructions for receiving, processing and inputting adverse drug reaction reports were completed as a normal function of the changes FDA has made to the system. They will be updated and revised as necessary.

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2. --Develop and implement specific criteria for the timely entry of new drug application status and assignment information into the New Drug Evaluation/Management Information System

We concur. As a result of FDA's evaluations of the system and user needs, rather than as a result of this audit, the NDE/MIS is currently undergoing major changes designed to correct problems of inaccuracies and untimeliness in the entry and retrieval of application status and assignment data. The completed implementation of these changes will encompass conversion to a data base management system allowing direct access. New manuals for data entry and retrieval are expected to be available by July 1986. It has also been decided to contract the data entry function, thereby decreasing the review decision burden for data entry and allowing concentration of effort on quality and completeness of data. This contract specifies criteria for the timely entry of information into the MIS system.

GAO Recommendation

3. --Perform a complete audit of the information in the Astro-IV system, specifically aimed at correcting the inactive ingredient data element.

Department Comment

We do not concur. As we stated in the General Comments above, while some Agency statements and documents may have led to a different perception, subsequent conversations with GAO were meant to explain the primary purposes of the Astro-IV Drug Information System. These are to support the Agency's reporting requirements under the Freedom of Information Act and the Drug Price Competition and Patent Restoration Act, to support product substitution programs at the State (Medicaid) and national (Medicare) levels, and to support the Maximum Allowable Cost (MAC) program for the Health Care Financing Administration. The validity of the data base for these programs is well established in the pharmaceutical industry and health care community. The consistently high standards of quality of these reports have withstood both marketplace and judiciary challenges. Correcting the historical (inactive) data base on inactive ingredients would not be cost effective because of its limited informational value. It should be noted, however, that two standard dictionaries, an ingredient dictionary and an applicant dictionary, have been developed and are being used for current entries of inactive ingredients. However, all data on currently marketed approved products has been reviewed and is considered to be close to 100 percent accurate.

GAO Recommendation

4. --Monitor the reliability of data in all three systems by periodically testing data input procedures and system output.

Department Comment

We concur. Periodic testing of inputs and output to the ADR system for accuracy and completeness will be initiated.

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Since 1978, the Agency has been periodically auditing and testing MIS data elements against those which also occur in Astro-IV. Another audit will be conducted within the next two years. During this period there will be an integration and sharing of the MIS and Astro-IV data bases. In the past, several data analyses were performed to identify discrepancies between the two systems. Corrections were limited to only higher priority data classes because of limited resources. Activities were necessarily restricted to areas of greatest payoff in both the agency programs and the health care community.

GAO Recommendation

5. --Implement standard drug terminology to enhance the integration of drug information systems.

Department Comment

We concur. FDA has been developing standard terminology for use in its ADP systems for a number of years as had been indicated to GAO. At this time, dictionaries have been developed and are being used for both the adverse drug reaction system and Astro-IV. An extensive drug name/ingredient dictionary and COSTART (coded standard adverse reaction terms) dictionary have been developed and are being used in the ADR system.

Several standardized dictionaries and tables are being used in Astro-IV. They include:

- Ingredient dictionary (both active and inactive) giving source of names (Merck, USAN) and synonyms
- Applicant/manufacturer dictionary
- Dosage form table
- Route of administration table
- Pharmacological activity table

Work is underway now to integrate the NDE/MIS and Astro-IV in the Centerwide ORACLE Management Information System (COMIS). Standards will be implemented throughout that system as well.

GAO Recommendation

6. --Identify and document reviewers' and managers' automation needs through a rational assessment and development process and develop systems that directly support the review and analysis of drug applications and the monitoring of approved drugs. As part of the assessment and development process, (1) evaluate the existing systems and determine if it would be more cost beneficial to enhance, replace, or scrap them and (2) evaluate the use of up-to-date technology to enhance data base integrity and to solve paper volume, handling, and storage problems.

Department Comment

We agree that assessment of reviewers' and managers' needs for automated systems is necessary, and FDA has conducted needs assessments

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over the past few years in which requirements analyses were performed for each of the three automated systems studied. An adverse reaction task force, led by senior managers from the adverse reaction program, a MIS improvement committee, and the Astro-IV effort on identifying ANDA-suitable products were conducted. The results of these, and other requirements analysis efforts have led to major improvements to both data identification and system utility.

As to evaluation of up-to-date technology, GAO was aware that several long range activities in FDA are directed toward information needs of drug application reviewers. A joint FDA-Pharmaceutical Manufacturers' Association Committee is exploring possibilities in this area. Decision support tools, based on new technologies, are being explored by a special staff in the Office of Management. In conjunction with drug applicants, FDA is conducting experiments seeking to determine the feasibility and benefits, if any, of the electronic transmission of clinical data for safety and effectiveness in drug applications. Additional experiments are planned for use of automated formats for data relating to chemistry, animal pharmacology/toxicology, statistics, pharmacokinetics, and bioavailability.

GAO Recommendation

7. --Prepare long-range automatic data processing plans to assist (1) in identifying the automated technology and information systems the Center needs to carry out its mission and in (2) justifying resulting budget requests.

Department Comments

Long range plans for systems development projects for Drugs and Biologics with respect to drug information systems have been in place since the mid-1970s. In addition, FDA completes a budget and ADP plan annually as part of the budget process. With guidance from the Department and from the Director, Information Resources Management, a more useful planning process has been implemented in keeping with Paperwork Reduction Act requirements and OMB Circular A-130. This new procedure is evident in the recently completed draft FY 88 Information Technology Systems Budget and the Five-Year Information Resources Management Strategic Plan for FY 88-92 for the Center for Drugs and Biologics as well as all other components of FDA. These plans are currently being finalized in a formal FDA Plan to conform with OMB Circular A-130, which was issued on December 12, 1985. FDA has acted expeditiously to implement Circular A-130, contrary to the implications in this report.

Prior to the issuance of Circular A-130, however, FDA routinely prepared five-year plans to support both systems development efforts and budget execution. These plans are viewed as an important activity in determining future ADP directions, and they also serve as budget documents for FDA and HHS management decisions concerning the commitment of resources.

The following are GAO's comments on the Department of Health and Human Service's letter dated July 18, 1986.

GAO Comments

1. The Department of Health and Human Services' general comments on clarifying this report's premises center on the Astro-IV System's role. The comments demonstrate that there is considerable confusion within FDA over that system's intended and actual role. After reading our draft report, a senior FDA official told us that the system was never intended for use by reviewers and that it is a "good system" in terms of its actual uses. However, several officials from the FDA information systems offices told us that an effort has been under way over the past 5 years to improve Astro-IV and to integrate it into the drug review process. In addition, agency documents support the argument that FDA has intended Astro-IV to be used for drug reviews. Because of this difference of opinion between several groups at FDA, we believe that FDA needs to assess Astro-IV and determine its use in the drug review process. Accordingly, we have changed our original recommendation that FDA correct Astro-IV data inaccuracies. We are now recommending suspension of further funding to improve this system's utility and accessibility for reviewers until the system is completely reviewed and a determination is made regarding FDA's objectives for it. (See page 41.) We maintain that, on the basis of a significant amount of testimonial and documentary evidence, FDA has pursued a course that demonstrates its intent that Astro-IV be used by reviewers.

Finally, we have clarified our conclusion on the "effect" of these unreliable systems on the review process. In our opinion, FDA's problems with automation are symptoms of an overall inability to properly manage drug information (see page 24) and not just problems with systems. Because of FDA's critical role in dealing with public health and safety, we believe that the problems found during our review are substantial. Taken together, the problems we cite with system reliability and utility, continuing use of manual procedures, paper load, and inefficient use of available technology can have undesirable effects on the drug review process. To clarify this point, we have changed the language in the executive summary to expand the scope of problems from just systems to all management of drug information. (See page 3.)

2. We acknowledge that the Astro-IV System supports a variety of agency programs not related to the new drug evaluation process. Furthermore, on the basis of interviews with a random sample of 60 new drug reviewers and an assessment of the system's data base, we agree

with FDA's implicit suggestion that Astro-IV provides little support to the new drug evaluation process.

However, the Department's comment that the Astro-IV System is intended to be of limited use to reviewers is not supported by FDA official statements, documentation, and actions. We were told by a senior FDA official that the following systems were "crucial" to the review process: Astro-IV, the Adverse Drug Reaction System, the New Drug Evaluation/Management Information System, and the Drug Registration and Listing System. Later, other officials also noted that Astro-IV was a "drug review" system. In addition, FDA officials noted that Astro-IV had problems, but that FDA was making a serious effort to make it useful for drug reviewers. Furthermore, in responding to our 1980 report, where we noted that reviewers were not using Astro-IV, the Department concurred with our assessment and agreed to "take steps to make appropriate information systems more accessible to reviewers." From that point on, without ever performing a comprehensive assessment of reviewers' needs, FDA took methodical steps to improve Astro-IV and make it more accessible to reviewers.

The evidence we collected demonstrates that FDA viewed Astro-IV as a drug review system and was actively taking measures to improve its ability to support the new drug review process. Every document we obtained that described Astro-IV noted that the system supports the drug review process. Specifically, every FDA budget request to the Congress from 1983 to 1987 states explicitly that Astro-IV "supports the new drug evaluation process." The 1985 and 1986 automatic data processing plans from information systems also stated that Astro-IV "maintains a file on IND's [Investigational New Drugs], NDA's [New Drug Applications], and ANDA's [Abbreviated New Drug Applications]," and added that "this system supports the review process, Freedom of Information and the Approved Prescription Drug Products." In addition, these plans also note the improvements being made in Astro-IV, many of which are designed to make the system more accessible and desirable for use by reviewers. For example, FDA improved the system's accessibility and ease of use by implementing a new software called Datatrieve, which allows users easier access to scientific data (see page 18.) Also, FDA improved the quality of the data base, and published a comprehensive users' manual that presents in detail the many features of the system. Finally, FDA officials and plans indicated that FDA is considering placing the Astro-IV System under Oracle, the data base that was used to upgrade and substantially improve the utility (for reviewers) of the Adverse Drug Reaction System. (See page 18.) Oracle is a powerful,

user-friendly data base management system that would do little to support the handling of Freedom of Information requests and the issuance of publications. FDA officials told us that this software was desirable because it would encourage reviewers to use the system.

We disagree with the Department's suggestion that the inactive ingredient file is seldom used. Our interviews with reviewers revealed that the few chemists who had used the system cited the inactive ingredient file as one from which they would seek information. In addition, according to one senior official, the Astro-IV System demonstrated its importance during the March 1984 controversy over E-Ferol, an injectable vitamin E solution that is allegedly linked to the deaths of over 30 premature infants. This official stated that drug reviewers searched Astro-IV on the emulsifier, the inactive ingredient solution used to "hold" the vitamin E, and found that Polysorbate 80 (an inactive ingredient) was used in an unusually high amount. This official also noted that FDA was investigating the possibility that this ingredient was linked to the drug's problems.

Furthermore, we agree that, until FDA categorically decides to use the system in drug reviews, it should not expend funds to correct the data problems revealed through our tests. Instead, we are recommending that FDA evaluate the Astro-IV System's role in its organization and decide how the system's considerable data are to be used. (See page 41 for our revised recommendation.) After a full assessment of the system and of reviewers' needs, FDA can properly decide whether to continue to maintain inactive ingredient data.

3. We agree that the most important source of drug review information concerning inactive ingredients comes from the application itself and that a reviewer would not rely solely on the Astro-IV data base. (We removed language on page 21 implying that a reviewer might use the system as the only source of information.) However, our conclusion on the importance of Astro-IV's inactive ingredients to the new drug approval process was based on interviews with drug reviewers, especially chemists who had used the system and who had noted the utility of this data. Furthermore, in an article published in a chemical information journal, the author (an FDA chemist) stated, "The Astro system...contains data which are being updated constantly and serve as essential tools in the review process.... Although I have touched on the aspects of the Astro search system only briefly, I emphasize its utility to the reviewing chemist." However, given FDA's considerable confusion over the use of this system in the drug review process, we believe that

FDA should reevaluate the necessity of entering inactive ingredients into Astro-IV and determine if this system or some other alternative should be used to assist new drug reviewers. (See revised recommendation on page 41.)

4. The fact that FDA made a policy decision concerning adverse drug reaction review is not pertinent to our report's discussion of the review program. Our discussion highlights the role of the adverse reaction reviewer as the "first line interpreter" of reports, not the 1983 policy decision. We present in some detail the important duties and responsibilities of the adverse reaction reviewers. (See page 33.) Furthermore, we describe at length how the reviewers in the Reports Evaluation Branch are responsible for collecting and analyzing critical information on adverse drug reactions, and then communicating that information to the new drug reviewing divisions. Reviewers in the Reports Evaluation Branch are working very hard to develop reports and analyses concerning the adverse reaction reports received at FDA. In addition, we explicitly stated that FDA has established formal procedures for the internal communication of adverse drug reaction information. (See page 33.) However, the Department's comments fail to note that regulatory authority for monitoring marketed drugs remains with the new drug reviewing divisions (21 Code of Federal Regulations 314). Under this authority, the reviewers in those divisions are ultimately responsible for making the decisions concerning such regulatory changes in labelling that could occur as a result of reported adverse reactions or approval for marketing. Therefore, it is imperative that adverse drug reaction information be adequately communicated to the new drug reviewing divisions.

During our review, it became apparent that a serious communications gap existed between the adverse reaction reviewers and the medical officers in the new drug reviewing divisions, despite the established safety conference procedures. Our interviews with medical officers in the drug review divisions did not support FDA's contention that adverse reaction information was being adequately communicated between the two groups. Several medical officers said that they seldom communicate with the reviewers in the Reports Evaluation Branch, and others indicated an unwillingness to communicate. (See page 34.) As we note in our report, one division director requires reviewers to ask if they can discuss adverse drug reaction issues with the branch. Another division director was explicit in criticizing the usefulness of information received from the Reports Evaluation Branch, echoing the concerns of some reviewers who felt that such information was not completely reliable.

Finally, at the time of our audit, our interviews indicated that medical officers were either unaware of, or unwilling to attend, scheduled safety conferences. While it is conceivable that these conferences are now working "remarkably well," as the Department states, the preponderance of evidence, including critical statements from division directors (see page 34), does not support the Department's argument.

5. Regardless of the differences between the types of evaluations performed by reviewers, regulatory authority over marketed drugs remains with the new drug reviewing divisions. Drug reviewers are responsible for ensuring that marketed drugs are properly labelled with known adverse reactions or possible safety risks.

6. Contrary to the implications in the Department's comments, we did not assess the quality of data received before January 1, 1980; nor did we ignore the improvements in the system or changes to processing procedures. At the outset, we agreed to test the reliability of data entered between January 1, 1980, and September 30, 1984, and to sample data entered after September 30, 1984. Our tests were designed to demonstrate the difference between the quality of the data under the old system (batch) and the new online system under Oracle. (See page 18.) Our tests revealed, and we stated (see page 19), that FDA did improve the system for data entered from reports received after September 30, 1984. However, data entered before that time either contained numerous errors or were incomplete. Although FDA changed its procedure (see page 26), this change did not eliminate the need for complete and accurate data prior to the change. FDA implicitly substantiated this position when it decided to put over 100,000 reports (starting with reports received after January 1, 1980) on line under this new system. If, as the Department indicated in its comments, it is not important for this data to be complete or accurate, then there seems to be little reason to spend the resources to place it on line for use by adverse drug reaction reviewers.

Finally, the Department incorrectly implies that we did not take into account certain changes to the agency's reporting requirements and the Adverse Drug Reaction System. We noted in the report that FDA has made changes in the processing and receipt procedures for adverse drug reaction reports (see page 26). In addition, we stated that we believe these changes will make the data base more complete. The actual date (August 23, 1985) of these processing changes is irrelevant, however, in terms of our assessment of the system's present reliability. The system itself was changed and upgraded (see page 19) on October 1, 1984, not on August 23, 1985, as stated by the Department in its comments. In

addition, the lack of completeness in the overall adverse reaction data base, as indicated in past GAO reports, internal FDA studies, and congressional hearings, has been a constant and critical problem at FDA. As indicated by our test, numerous reports sent to FDA after January 1, 1980, have not been entered into the system. The volume of missing reports, ranging from 25,000 to 40,000, prevents us from stating that the system is now completely reliable (see page 20) despite the processing changes.

7. We gave FDA credit for improvements in the Adverse Drug Reaction System's accuracy rate (see page 19).

8. The Department's comments are contradictory. The agency states that a 100-percent accuracy rate is "impossible" while attempting to claim that the current error rate for several adverse reaction data elements is less than 1 percent (or close to 100 percent accurate). The criteria for 100-percent accuracy and completeness are based on statements from several FDA senior officials. As we cited on page 20, these officials told us that because these systems can potentially affect the public health and welfare, they must be 100 percent complete and accurate. While we agree that this reliability rate may be difficult to achieve, it does represent the only standard given to us by FDA officials against which the results from our tests could be applied. Therefore, we determined that all errors discovered in the system, except for those involving the drug manufacturer's identification, were significant and contributed to the system's lack of reliability. Furthermore, we defined the term "inaccuracy" by specifically highlighting the definition of a system error in footnote 9. (See page 19.)

Finally, regarding the Department's comment on the systems' inaccuracies, FDA's list of "key accuracy data" is not consistent with the data required by FDA's own review procedures. These procedures identify the dosage data element as important because of its utility in assessing causality (see page 19). Specifically, according to FDA's Procedure Manual for Handling Drug Experience Reports, the minimum information desirable for processing a report and determining causality includes "drug, indication and dose." Also, according to our interviews with adverse drug reaction reviewers, causality is one of the first areas a reviewer analyzes.

9. We agree that FDA has begun to make significant changes in the way it manages its information resources. Throughout the report, we acknowledge the progress that it has made in improving such information systems as the Adverse Drug Reaction System, Astro-IV, and the New Drug

Evaluation/Management Information System. In addition, we note the organizational changes FDA effected regarding the establishment of an Office of Information Resources Management. However, it is significant to note that these major organizational changes did not occur until August 1985, nearly 5 years after the passage of the Paperwork Reduction Act. During that time, FDA endured a series of crises related to its management and use of drug information, revealing the inadequacy of FDA's use of information in reviewing new drugs and monitoring marketed drugs. The Zomax and Oraflex hearings, which gave rise to this audit, demonstrated FDA's propensity to be reactive in the face of drug controversies. We believe that the changes made in 1984 and 1985 were due to the new Commissioner's desire to bring FDA to the automation forefront and to have the agency be "proactive" in the management of its information resources. Until that time, there is little evidence showing that either the Department of Health and Human Services or FDA was taking an overall approach to resolving systemic problems in the agency's management of information resources.

In addition, our criticism of FDA's information resources management practices is linked to the agency's continuing difficulties in developing systems that meet the needs of its reviewers. Since our last report on the drug review process in 1980, FDA has not assessed the automation needs of new drug reviewers. Instead, it has relied on an incremental approach to augmenting such systems as Astro-IV. According to our interviews with senior level managers, FDA did not make a decision on the exact purpose of Astro-IV. Instead, it attempted to encourage reviewers' use of the system by improving data quality, implementing user-friendly software, and upgrading hardware. If FDA had followed sound information resources management practices, including compliance with the Federal Information Resources Management Regulation, it would have begun an assessment of reviewers' needs immediately after the 1980 report. According to our interviews with over 60 interviewers, however, FDA had made no progress in introducing automation to the new drug evaluation process.

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