



DEC 14 1999

Memorandum

Date *Michael Mangano*
For June Gibbs Brown
From Inspector General

Subject Review of the Food and Drug Administration's Handling of Adverse Drug Reaction Reports (CIN: A-15-98-50001)

To Jane E. Henney, M.D.
Commissioner of Food and Drugs

The attached final report presents the results of the Office of Inspector General's review of the Food and Drug Administration's handling of adverse drug reaction reports. This review was requested by Senator Edward M. Kennedy in a letter to the Secretary of Health and Human Services.

If you have any questions, please call me or have your staff contact Joseph J. Green, Assistant Inspector General for Public Health Service Audits, at (301) 443-3582. Please refer to Common Identification Number A-15-98-50001 in all correspondence relating to this report.

Attachment

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**REVIEW OF THE FOOD AND DRUG
ADMINISTRATION'S HANDLING OF
ADVERSE DRUG REACTION REPORTS**



**JUNE GIBBS BROWN
Inspector General**

**DECEMBER 1999
A-15-98-50001**

EXECUTIVE SUMMARY

BACKGROUND

The mission of the Food and Drug Administration's (FDA) human drugs program is to assure that safe and effective drugs are available to the American people. A vital part of this mission is the continuous monitoring of the safety of drugs after they are approved for marketing by evaluating reports of adverse drug reactions (ADR)¹ and taking appropriate regulatory action when needed. The reporting of ADRs by hospitals, health professionals, and consumers is strictly voluntary. Reports may be sent directly to FDA, to the manufacturer, or to both. When manufacturers receive these reports, they are required by regulation² to report them to FDA.

Essential information from the ADR reports is entered into an FDA data base called the Adverse Event Reporting System (AERS). The ADR reports are then analyzed by FDA post-marketing drug risk assessors in FDA's Office of Post-Market Drug Risk Assessment (OPDRA) to identify serious,³ unexpected adverse reactions that were not included in the drug's labeling when the drug was approved or in subsequently revised current labeling. Summaries of these analyses, referred to as monitored adverse reactions (MARs), are provided to FDA's review divisions that have regulatory responsibility for new drug approval and safety. Pharmacoepidemiological⁴ studies are also provided to the review divisions for use in regulatory action. Regulatory action taken in cooperation with the drug's sponsor may include: (1) adding the newly discovered adverse reaction to the drug's labeling; (2) sending letters to health professionals advising them of the adverse reaction; (3) restricting distribution and use of the drug; or (4) withdrawing the drug from the market.

¹ An adverse drug reaction is any adverse event associated with the use of a drug in humans, considered at least possibly to be drug related, including the following: an adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from a drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

² 21 Code of Federal Regulations (C.F.R.) Part 310; Section 310.305
21 C.F.R. Part 314; Section 314.80

³ Serious means any adverse drug experience occurring at any dose that results in any of the following outcomes: death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect.

⁴ Pharmacoepidemiology is the study of the use of, and the effects of, drugs in large numbers of people.

OBJECTIVE

The objective of our review was to answer Senator Kennedy's questions included in an August 27, 1998 letter to the Secretary of the Department of Health and Human Services (HHS) regarding FDA's handling of reports of adverse reactions to marketed drugs.

SUMMARY OF FINDINGS

Senator Kennedy's questions and our responses can be categorized and summarized as set forth below. We have cross-referenced the following summaries to the related questions and responses presented in the body of this report.

- ***ADR reporting process*** - The ADR reporting process is voluntary by design. It has been enhanced during the 1990's principally by: the creation of MedWatch to increase the number of health professionals reporting serious adverse reactions to, and problems with, FDA-regulated products; the implementation of AERs to more fully computerize the receipt and analysis of ADRs; and the formation of OPDRA to monitor the safety of marketed drugs. (See questions 1 and 2, page 5.)
- ***Adequacy of ADR policies and procedures*** - The policies and procedures for receiving ADRs appear adequate. However, the coordination between post-marketing drug risk assessors and review divisions responsible for drug approval and safety needs to be improved to expedite regulatory action. In addition, no quality assurance system exists to ensure the detection of signals or patterns of serious, yet unrecognized ADRs that might indicate a public health problem. (See question 3, page 7.)
- ***Percentage of ADRs reported to FDA*** - Based on the incidences of ADRs estimated in the medical literature, FDA receives a low percentage of ADR reports. Because its post-marketing surveillance system is not designed to gauge the incidence of ADRs, FDA does not know the magnitude of the ADR problem nor whether progress is being made in reducing the number of serious ADRs. The agency can avail itself of several opportunities to increase the number and quality of ADR reports. (See questions 4 and 5, page 10.)
- ***Adequacy of resources for ADR handling*** - If FDA continues to conduct its ADR report handling in the same manner as it has over the years, the current level of resources allocated for ADR report handling is probably sufficient. However, as more drugs are approved for marketing and new initiatives are implemented, the agency will have to step up its monitoring responsibilities and additional resources will likely be needed. (See questions 6 and 7, page 17.)
- ***Manufacturer compliance with ADR regulations*** - The FDA has increased the number of ADR inspections at manufacturer facilities, and, according to the Agency's

classification of these inspection reports, manufacturers appear to be in compliance with reporting requirements. (See questions 8 and 9, page 19.)

RECOMMENDATIONS

We recommend that the Commissioner of Food and Drugs:

1. Develop policies and procedures for more effective coordination between FDA post-market drug risk assessors and FDA's review divisions to better ensure that prompt and appropriate regulatory action is taken when necessary on those drugs identified in MARs.
2. Develop and implement a quality control system to ensure that signals of serious, yet unrecognized drug-associated adverse reactions that might indicate a public health problem are not overlooked.
3. Develop and apply methodologies to quantify the extent and scope of the ADR problem with the goal of reducing the occurrences of serious preventable ADRs.
4. Encourage greater interactive reporting of serious ADRs and product problems by health professionals directly to FDA by telephone to ensure that accurate and essential information necessary for regulatory action is received by the agency in a timely manner.
5. Coordinate with the Health Care Financing Administration (HCFA) to require hospitals to report all serious, unexpected ADRs directly to FDA as a condition for participation in Medicare and Medicaid.
6. Explore pro-active methods to obtain ADR data to supplement the agency's passive post-marketing monitoring system.
7. Systematically evaluate the adequacy of post-marketing surveillance staffing levels necessary to effectively monitor the safety of the increasing number of marketed drugs and, as necessary, identify funding sources for additional staff.

AGENCY COMMENTS AND OIG RESPONSE

In its November 12, 1999 memorandum commenting on our draft report, dated August 4, 1999, FDA agreed with our recommendations and stated that it was taking or planned to take actions to strengthen the ADR reporting and handling process.

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INTRODUCTION

BACKGROUND

The FDA is responsible for approving the marketing of new drugs--a determination based on the drug's benefits outweighing its risks. Because all risks are not known until after a drug is in greater use after marketing, FDA has a post-market surveillance system designed to, among other things, receive, analyze, and act upon reports of ADRs. The agency also has contracts with groups to augment its post-market surveillance data.

New Drug Approval Process

In deciding whether to approve a new drug for marketing, FDA must determine whether the drug's benefits outweigh its risks. This determination is based on pre-market clinical studies in which the new drug is tested on a few thousand people or less. The FDA acknowledges that pre-market studies have inherent limitations, such as size constraints, narrow populations, and relatively short durations. The result of these limitations is that rare adverse reactions, drug interactions, adverse effects in special populations, and adverse effects occurring after prolonged use cannot be reliably detected during the study period. It is generally recognized that once a drug is on the market and in greater use, many people gain the expected benefits from the drug, while a certain segment will experience adverse reactions--some very serious. Because important information about a drug's safety may become available after marketing approval, FDA believes that post-market surveillance--including the receipt and analysis of ADR reports--is an integral part of drug regulation.

Overview of FDA's Handling of ADR Reports

By law, FDA's Center for Drug Evaluation and Research (CDER) is responsible for overseeing the safety and efficacy of drugs from the time they are being tested to the post-market period. Among CDER components are 15 divisions to review new drugs and OPDRA to monitor the safety of marketed drugs, including the handling of ADR reports. The review divisions are substantially supported by user fees paid by drug sponsors that submit new drug applications, while OPDRA is financed through annual Congressional appropriations.

The reporting of ADRs to FDA by hospitals, health professionals, and consumers--all key players in the ADR arena--is strictly voluntary. Reports may be sent directly to FDA's MedWatch office, which was established in the Office of Commissioner in 1993⁵ to promote and facilitate voluntary reporting of serious ADRs by health professionals; to the manufacturer; or to both. When manufacturers receive these reports, they are required by

⁵ On July 5, 1999, the MedWatch program was reassigned from the Office of Commissioner to CDER.

regulation to report them to FDA. In 1997, manufacturers submitted approximately 190,000 ADR reports.

Essential information from the ADR reports is entered by contractor personnel into a computerized data base system called AERS; and OPDRA risk assessors then analyze the ADR reports to identify serious, unexpected adverse reactions that were not included in the drug's labeling when the drug was approved or in subsequently revised current labeling. The OPDRA provides summaries of these analyses, referred to as MARs, to FDA's review divisions that have regulatory responsibility for drug approval and safety.

Pharmacoepidemiological studies are also provided to the review divisions for use in regulatory action. During these processes, before regulatory action is taken, FDA attempts to determine that the drug itself, rather than other underlying factors, caused the adverse reaction. Regulatory action taken in cooperation with the drug's sponsor may include:

(1) adding the newly discovered adverse reaction to the drug's labeling, an action estimated to occur with more than 50 percent of drugs after they are approved; (2) sending letters to health professionals advising them of the adverse reaction; (3) restricting distribution and use of the drug; or (4) withdrawing the drug from the market. Regarding the latter regulatory action, between September 1997 and September 1998, 5 prescription drugs⁶ were removed from the market by their manufacturers due to unexpected serious adverse reactions.

The OPDRA and CDER's Office of Compliance work together to identify drug manufacturers that should be inspected for poor performance in ADR reporting. The Office of Compliance then issues assignments to the appropriate FDA district offices located throughout the United States (U.S.) to conduct inspections of manufacturers' records for compliance with applicable ADR reporting requirements.

Cooperative Agreements and IMS Health Contract

The FDA currently supports five different pharmacoepidemiological research groups through a cooperative agreement arrangement at a 3-year cost of about \$3 million. These cooperative agreements allow the agency access to a wide range of different types of data for post-market surveillance. The FDA has also awarded a 3-year contract (January 1, 1998-December 31, 2000) at a cost of \$850,000 per year to IMS Health. The IMS Health data is used to identify patterns of drug usage, and describe user populations and prescribing practices. The data base is also used to conduct population-based risk assessments and pharmacoeconomic assessments.

⁶ Fenfluramine (marketed as Pondimin) and Dexfenfluramine (marketed as Redux), two diet drugs associated with heart valve problems; Terfenadine (marketed as Seldane), an antihistamine that resulted in fatal interactions with other drugs; mibefradil (marketed as Posicor), a blood pressure medicine that caused potentially harmful interactions with a large number of other drugs; and bromfenac sodium (marketed as Duract), a painkiller found to cause severe, sometimes fatal, liver damage when used for a period longer for which it was approved.

OBJECTIVE, SCOPE, AND METHODOLOGY

Objective and Scope

The objective of our review was to answer Senator Kennedy's questions included in an August 27, 1998 letter to the Secretary of HHS regarding FDA's handling of reports of adverse reactions to marketed drugs.

Our review focused on FDA's handling of reports of adverse reactions to marketed prescription drugs and did not include adverse reactions to other products regulated by FDA, such as biologics, devices, animal drugs, and foods. For the category of products we focused on, we did not evaluate the appropriateness of FDA's regulatory decisions made on the basis of information contained in either ADR or MAR reports. Our review also did not include examining FDA's handling of reports of medication errors, which can occur when prescribing, repackaging, dispensing, or administering a product.

Methodology

To accomplish our objective, we:

- ▶ Reviewed laws, regulations, policies, and procedures applicable to FDA's responsibilities for monitoring the safety of marketed drugs.
- ▶ Reviewed FDA internal reports and reports prepared outside the agency on FDA's post-market drug safety surveillance system.
- ▶ Reviewed scientific articles on ADRs and drug safety published in various medical journals including the *Journal of the American Medical Association (JAMA)*, *The Annals of Pharmacotherapy*, and *Pharmacoepidemiology and Drug Safety*.
- ▶ Held discussions with FDA staff involved in all aspects of monitoring the safety of marketed drugs including ADR post-marketing drug risk assessors, epidemiologists, MedWatch officials, compliance personnel, and experts on drug safety outside FDA.
- ▶ Reviewed summary statistical reports on ADRs, as well as individual ADR reports submitted to FDA by health professionals, consumers, and manufacturers. Examined various MARs and attended an FDA conference where MARs were discussed.
- ▶ Interviewed experts on drug safety on the faculty of Georgetown University.

- ▶ In February 1999, attended a conference on ADRs sponsored by the Drug Information Association and the General Accounting Office.
- ▶ Reviewed an internal publicly issued report developed by FDA in May 1999 regarding managing risks from medical product use.

Our review of internal controls was limited to gaining an understanding of and observing the processes that FDA has in place for the receipt, processing, and analysis of ADR reports. We conducted our review in accordance with generally accepted government auditing standards. Our review was performed at FDA Headquarters in Rockville, Maryland, from May 1998 to May 1999.

RESPONSES TO SENATOR KENNEDY'S QUESTIONS AND OIG ANALYSIS OF RELATED ISSUES

Senator Kennedy's questions and our responses can be categorized and summarized as set forth below. We have cross-referenced the following summaries to the related questions and responses presented in the body of this report.

- ***ADR reporting process*** - The ADR reporting process is voluntary by design. It has been enhanced during the 1990's principally by: the creation of MedWatch to increase the number of health professionals reporting serious adverse reactions to, and problems with, FDA-regulated products; the implementation of AERs to more fully computerize the receipt and analysis of ADRs; and the formation of OPDRA to monitor the safety of marketed drugs. (See questions 1 and 2, page 5.)
- ***Adequacy of ADR policies and procedures*** - The policies and procedures for receiving ADRs appear adequate. However, the coordination between post-marketing drug risk assessors and review divisions responsible for drug approval and safety needs to be improved to expedite regulatory action. In addition, no quality assurance system exists to ensure the detection of signals or patterns of serious, yet unrecognized ADRs that might indicate a public health problem. (See question 3, page 7.)
- ***Percentage of ADRs reported to FDA*** - Based on the incidences of ADRs estimated in the medical literature, FDA receives a low percentage of ADR reports. Because its post-marketing surveillance system is not designed to gauge the incidence of ADRs, FDA does not know the magnitude of the ADR problem nor whether progress is being made in reducing the number of serious ADRs. The agency can avail itself of several opportunities to increase the number and quality of ADRs. (See questions 4 and 5, page 10.)
- ***Adequacy of resources for ADR handling*** - If FDA continues to conduct its ADR report handling in the same manner as it has over the years, the current level of

resources allocated for ADR report handling is probably sufficient. However, as more drugs are approved for marketing and new initiatives are implemented, the agency will have to step up its monitoring responsibilities and additional resources will likely be needed. (See questions 6 and 7, page 17.)

- ***Manufacturer compliance with ADR regulations*** - The FDA has increased the number of ADR inspections at manufacturer facilities; and, according to the agency's classification of these inspection reports, manufacturers appear to be in compliance with reporting requirements. (See questions 8 and 9, page 19.)

For each question or group of questions posed by Senator Kennedy, we present a brief summary of our findings followed by additional details.

Questions 1 and 2: What is the current process FDA uses to receive and analyze ADR reports, and has this process changed in the last several years, if at all?

The FDA's overall process for receiving ADR reports is based on initial voluntary reporting on the part of health professionals, and this voluntary nature has not changed since 1961. However, FDA has made some modifications to its system, including: creating MedWatch in 1993 to enhance voluntary reporting by health professionals; implementing AERS in 1997 to stimulate electronic ADR reporting by manufacturers and to make the latest technology available for ADR analysis; and establishing OPDRA in 1998 and elevating it within FDA's organizational structure.

***RECEIPT OF ADRs--A SYSTEM BASED
ON VOLUNTARY REPORTING***

Health professionals voluntarily report ADRs either directly to FDA, to the manufacturer, or to both.

Health Professionals--Direct Reporting to FDA

The ADR reports submitted by physicians and other health professionals⁷ are strictly voluntary and are termed spontaneous in that they derive from usual clinical practice as opposed to originating from a clinical trial or medical literature. The ADRs can be reported directly to FDA by mail, fax, telephone, or via the Internet. According to FDA, Internet reporting is being revamped to make it more user friendly. From June 1, 1997, to May 31, 1998, FDA received 13,825 ADR reports directly from health professionals and consumers including 2,083 from the approximately 700,000 physicians in the U.S.

⁷ The FDA encourages consumers to report serious ADRs to their physicians. However, if desired, consumers may report ADRs directly to FDA.

Manufacturer Reporting to FDA

When manufacturers receive voluntary reports of ADRs from health professionals, they are required by regulation to submit them to FDA. Reports of serious, unexpected ADRs must be submitted to FDA within 15 calendar days of receipt. These are called 15-day reports. Reports of other ADRs, such as those considered not serious or those considered serious adverse reactions that are already identified on the drug's label, must be reported every 3 months for the first 3 years of marketing and annually thereafter. These are called periodic reports.

When additional information is needed on an ADR, manufacturers submit to FDA follow-up reports to the original report. These are called follow-up reports. In 1997, manufacturers submitted 36,783 15-day reports, 137,721 periodic reports, and 12,559 follow-up reports to FDA.

THREE SIGNIFICANT MODIFICATIONS MADE TO THE ADR PROCESS

The FDA has made some modifications to its system, including: creating MedWatch in 1993 to enhance voluntary reporting by health professionals; implementing AERS in 1997 to stimulate electronic ADR reporting by manufacturers and to make the latest technology available for ADR analysis; and establishing OPDRA in 1998 and elevating it within FDA's organizational structure.

MedWatch

The FDA established MedWatch in 1993 to enhance the effectiveness of post-marketing surveillance of drugs and other medical products as they are used in clinical practice and to help in the rapid identification of significant health hazards associated with these products. Among its activities, MedWatch operates a single system to make it easier for health professionals to report adverse events and other problems with FDA-regulated products to the agency. Following implementation of MedWatch, direct ADR reports to FDA increased from 7,640 in 1993-1994 to 13,825 in 1997-1998.

AERS

In late 1997, FDA created AERS--a state-of-the-art computerized information system designed to support and strengthen the post-marketing surveillance of human drugs. According to FDA, AERS is the result of efforts to implement many agreements from the International Conference on Harmonization as well as new regulations and pharmacovigilance processes of the agency to increase the efficiency with which CDER receives, files, and analyzes ADR reports. One of the goals of AERS is to allow for electronic submission of ADR reports by manufacturers, and the agency plans to require electronic submissions of ADRs from all drug

manufacturers. The FDA has proposed a 4-year phase-in period for electronic submission of ADRs. As of February 1999, 13 of approximately 220 companies were participating in the electronic submission pilot program.

OPDRA

In 1998, FDA established a new office--OPDRA--to monitor the safety of marketed drugs and to elevate this organization from a division to an office level in CDER. Within OPDRA, two divisions of Drug Risk Assessment (I and II) were created in which epidemiologists and risk assessors--once in separate units--were combined to bring their individual discipline expertise to the overall process of assessing drug risk data. Additional epidemiologists and drug risk assessors were also hired to staff these divisions.

Further information regarding OPDRA's resources is included in responses to Questions 6 and 7.

Question 3: Does FDA have adequate policies and procedures for receiving, processing, and analyzing ADRs?

The FDA appears to adequately receive and process the ADR reports it receives; however, it can improve the process for analyzing ADRs by ensuring better coordination between the risk assessors and the staff of the new drug review divisions, and creating a quality control system to ensure that all ADR signals are properly addressed.

RECEIPT AND PROCESSING OF ADRs APPEAR ADEQUATE

Our review and observation of the receipt and processing of ADRs showed that these activities, performed under contract with PSI International, appear to be adequate. The contractor has appropriate policies and procedures for receiving, distributing, tracking, controlling, and imaging ADR reports into AERS and through the post-marketing surveillance process. Standard operating procedures have been implemented for the following activities: (1) central triage unit (sorting and allocation of reports); (2) tracking and accountability system; (3) processing of expedited reports; (4) document control procedures for periodic reports; (5) imaging (the process of transferring hard copy ADR reports to electronic files); and (6) post-processing of individual safety report images.

In order to keep up with the volume of ADR reports, the contractor enters data 24 hours a day, 6 days a week. The ADR reports are entered into AERS in order of importance. Priority is given to 15-day reports from drug manufacturers and direct reports from health professionals and consumers. Following data entry, these reports are then routed to post-marketing drug risk assessors in OPDRA for analysis.

ANALYSIS OF ADR REPORTS CAN BE IMPROVED

We identified two serious shortcomings in FDA's methods for analyzing ADR reports:

- ▶ there is poor tracking and coordination of MARs forwarded by the risk assessors to the review divisions; and
- ▶ there is no quality control system to ensure that all ADR patterns that might signal a public health problem are detected.

Poor Tracking and Coordination of MARs

One of the risk assessors' key responsibilities is to critically review ADR reports and submit MARs to the review divisions, yet there is no tracking system to determine how the MARs are subsequently used by the divisions in making regulatory decisions. Further, the review divisions do not maintain records as to how the MARs are used, if at all. If MARs for potentially harmful drugs are not used, a considerable amount of time and effort is wasted in their preparation; and, more importantly, timely and effective regulatory action, such as labeling changes, may not be taken which could prevent additional occurrences of the adverse reaction.

We specifically noted that there is no coordination between OPDRA and the review divisions as to: (1) the specific information that must be uniformly provided in the MAR; (2) the point in time that a MAR should be submitted; and (3) the type of records that should be kept and by whom to show the disposition of each MAR. As a result of this lack of information, the risk assessors generally do not receive feedback from the review divisions as to the disposition of their MARs--275 of which were forwarded to the review divisions during the 6-year period from 1993 through 1998.

Without concrete data on the MAR process, we thus attempted to determine the MAR's usefulness through interviews with OPDRA officials and by attempting to ascertain the disposition of MARs in the review divisions. One OPDRA official noted that review divisions, which approve the marketing of new drugs based on the results of controlled clinical studies, tend not to rely on MARs, which primarily consist of anecdotal case studies, in determining how to handle a drug with reported adverse reactions. This official pointed out that it may be difficult for a review division, responsible for drug approvals, to appreciate another group of professionals forwarding them information that may poorly reflect on their decision to approve a new drug for marketing.

In our evaluation of the disposition of MARs in the review divisions, we determined that there is no consistency as to how MARs are used or how MAR information is processed. We also

identified no consistency among the review divisions concerning the regularity of scheduled safety conferences where ADRs are discussed. For example, we noted that some review divisions hold safety conferences on a routine basis; some on an ad hoc basis; and some do not hold safety conferences at all.

The Deputy Director for Review Management of CDER, conceding there are problems with the tracking and coordination of MARS, stated that policies and procedures are being developed to provide a more seamless process between OPDRA and the review divisions and to enhance the feedback loop regarding the use of MARS.

No Quality Control System to
Ensure ADR Signals are not Overlooked

The OPDRA does not have a quality control system to ensure that all ADR patterns that might signal a public health problem are detected. Such a quality control system would provide assurance that all ADR patterns that might signal a public health problem are detected by risk assessors as soon as possible and communicated to the review divisions for regulatory action. An internal FDA review, conducted in 1993, noted this weakness and raised concern that only one person was conducting reviews of ADRs for a certain drug or class of drugs and, therefore, something might be overlooked.

Currently, OPDRA risk assessors specialize in specific categories of drugs to be monitored, with no oversight by a quality control function. For example, one risk assessor is responsible for monitoring all pulmonary, reproductive, and urologic drugs; one is responsible for monitoring all metabolic and endocrine drugs; and another is responsible for monitoring all gastrointestinal, coagulation, and systemic antifungal drugs. In performing their roles, risk assessors must scrutinize ADR data in both AERS and individual reports to detect signals of serious, yet unrecognized drug-associated events. While productivity reports that risk assessors currently provide to OPDRA management generally indicate the number of ADR reports reviewed, they do not include sufficient information to assure management that ADR patterns for those drugs that might signal a public health problem have not been overlooked.

We share FDA's concern about individual reviews potentially missing important signals and believe that the agency should implement a quality control system to ensure that all potential safety problems are identified. Our concern is further amplified given that the workload of risk assessors has increased substantially since that 1993 report. For example, the number of direct and 15-day reports (initial and follow-up) evaluated by risk assessors has increased from 35,576 in 1993 to 80,793 in 1998, representing a 127 percent increase.

Questions 4 and 5: What percentage of ADRs are being reported to FDA and can FDA do more to improve that percentage?

It is not possible to accurately estimate the percentage of ADRs being reported to FDA because it is not known at this time the magnitude of the ADR problem. There is, however, general consensus that a low percentage of ADR reports is being sent to FDA; and that the agency can do more to ensure that it receives not only a higher number of ADRs, but also those that are of a higher quality to be used for analysis. Below we discuss:

- ▶ The fact that the actual ADR incidence is not known;
- ▶ The issue of low percentage of reporting to FDA; and
- ▶ Ways FDA can improve the reporting rate.

ACTUAL INCIDENCE OF ADRs IS NOT KNOWN--ESTIMATES VARY

Because FDA's system was designed only to detect signals of drug-related problems through voluntary reporting, it does not have ADR incidence data that would allow gauging of the extent of the ADR problem. Without such FDA data, we analyzed relevant studies, which showed various estimates of the problem, but generally concluded that ADRs present a significant public health problem in the U.S.

Even though it is the principal consumer protection agency in the Federal Government, FDA does not have a comprehensive system in place to accurately identify the number of adverse events that are associated with the use of FDA-regulated products, nor to evaluate the cause of these incidents and the strategies to avoid similar future incidents from occurring. Yet, FDA acknowledges that ADRs are a problem. In a May 1999 article published in *JAMA*, FDA officials cite data published in the ADR area and state that "expected toxic effects from marketed drugs, even when used appropriately, is estimated to rank among the top 10 causes of death in the U.S. and is estimated to cost more than \$30 billion annually."⁸

Absent FDA data on the magnitude of the ADR problem, we consulted various studies, which have estimated that as many as 1.4 million Americans are hospitalized each year because of serious adverse reactions to marketed drugs and that ADRs may also cause about 106,000 deaths. Conversely, other experts believe these numbers are much lower. Some of the published studies are listed below:

⁸ *JAMA*, May 12, 1999-Vol. 281, No. 18.

- ▶ A study published in *JAMA*⁹ estimated that in 1994, 2.2 million hospital patients had serious ADRs and 106,000 had fatal ADRs even though the drugs were correctly prescribed and properly taken. The study analyzed 39 previous studies of ADRs that occurred in U.S. hospitals over a period of 32 years.
- ▶ A study published in *The Annals of Pharmacotherapy*¹⁰ estimated that 5 percent of all hospital admissions have been identified as a result of ADRs, but that the true percentage may be much higher. The study included ADR rates from 49 hospitals or groups of hospitals both within and outside the U.S. When data for only U.S. hospitals were used,¹¹ we determined that 4.2 percent of admissions were the result of ADRs. According to the American Hospital Association, there were 33.2 million hospital admissions in 1993. Therefore, according to the study, approximately 1.4 million admissions were due to ADRs.
- ▶ A study published in *JAMA* in December 1997,¹² and subsequently cited in the March/April 1998 issue of *FDA Consumer*, an FDA publication, estimated that adverse reactions to drugs and biologic agents affect between 15 and 30 percent of hospitalized patients; and up to 29 percent of outpatients require hospitalization for ADRs.

With respect to the April 15, 1998 *JAMA* article, some believe that the number of deaths estimated in the study was high because most of the data were too old. The Pharmaceutical Research and Manufacturers of America (PhRMA), an organization representing many drug manufacturers, stated that if the study authors had applied the level of 1990's fatal ADRs to the 1994 hospital population, as opposed to the 30-year average, the estimated annual fatalities from ADRs would have been 24,000.

In another *JAMA* article,¹³ a health policy expert stated that a rational program to monitor the risks of marketed drugs ought to begin with reliable annual estimates of deaths and serious injuries from prescription drugs and information about the likely causes. This expert said that without such data, it is impossible to determine whether serious injuries associated with

⁹ *JAMA*, April 15, 1998-Vol. 279, No. 15

¹⁰ *The Annals of Pharmacotherapy*, 1993 July/August, Vol. 27

¹¹ Using the study data, we calculated that of the 42,745 admissions to 26 U.S. hospitals or groups of hospitals, 1,776 (4.2 percent) were the result of ADRs.

¹² *JAMA*, December 10, 1997-Vol. 278, No. 22

¹³ *JAMA*, May 20, 1998-Vol. 279, No. 19.

prescription drug adverse effects are declining, or whether an epidemic of drug-induced injury may be occurring.

Because of the varying estimates of ADRs, we believe that FDA, as the principal consumer protection agency of the Federal Government, should develop its own methods to determine the actual number of serious injuries and deaths caused by ADRs each year and take steps to reduce these numbers. In developing these methods, FDA should consider coordinating with the Centers for Disease Control and Prevention's National Center for Health Statistics, the Federal Government's principal health statistics agency.

LOW REPORTING OF ADRs TO FDA

Compared to the number of serious ADRs estimated in the scientific literature, the number of ADR-related deaths and hospitalizations reported to FDA is relatively low. The table below shows the number of suspected drug-related deaths and hospitalizations reported to FDA, both directly and through the manufacturer, for the 8-year period from 1990 to 1997.

Deaths and Hospitalizations Reported to FDA Between 1990 and 1997		
<i>Year</i>	<i>Deaths</i>	<i>Hospitalizations</i>
1990	3,957	12,491
1991	4,459	13,332
1992	5,902	16,942
1993	6,566	21,119
1994	7,931	23,890
1995	7,127	24,228
1996	8,160	26,847
1997	9,961	33,541

These numbers are significantly lower than the estimates of hospitalizations and deaths due to ADRs published in medical journals. For example, in 1994, the year used as the basis for the estimates in the April 1998 *JAMA* article, FDA received about 8,000 reports of deaths due to ADRs, while the *JAMA* article estimated that 106,000 deaths occurred that year. Similarly, for hospitalizations, FDA received almost 24,000 such reports in 1994, while the *Annals of Pharmacology* article estimated about 1.4 million. Further, even using the PhRMA-adjusted figures for the deaths due to ADRs--24,000--we still note a low reporting rate:

7,931 (reported to FDA in 1994) divided by 24,000 (the adjusted death rate for 1994 according to PhRMA) equals 33 percent.

FDA CAN IMPROVE ADR REPORTING RATES

The FDA recognizes that its existing passive reporting systems are not adequate to gauge the scope of these problems. We agree with FDA and believe it can do more to increase the number and quality of ADRs by, for example:

- ▶ Encouraging health professionals to directly report by telephone;
- ▶ Coordinating with HCFA to require hospitals to report serious, unexpected ADRs as a requirement for participating in Medicare/Medicaid;¹⁴ and
- ▶ Implementing pro-active reporting of ADRs to supplement the current passive reporting system.

Voluntary Reporting of ADRs By Health Professionals

Within the current voluntary ADR system, FDA believes that health professionals, most notably physicians and pharmacists, provide the highest quality ADR reports; yet, these groups have historically submitted extremely low numbers of reports to FDA. Further, the majority of health professionals, when they do report, are not using one of the most efficient methods--the telephone. According to FDA, less than 3 percent of reports of adverse reactions to FDA-regulated products are received by telephone.

Physician Reporting

Although there are more than 700,000 practicing physicians in the U.S., this group reported only 2,083 ADRs directly to FDA between June 1997 to May 1998, a period when more than 2.5 billion prescriptions were dispensed. This significantly low reporting rate prevents FDA from being aware of the magnitude of the ADR problem. According to FDA, direct reporting by physicians is the most efficient means by which the agency obtains information on new ADRs. Clinical data submitted in direct reports from health professionals are often more complete than data submitted by manufacturers because the reporting clinician has immediate

¹⁴ The HCFA administers Medicare, the nation's largest health insurance program, which covers 37 million Americans. Medicare provides health insurance to people age 65 and over, to those who have permanent kidney failure, and to certain people with disabilities. Medicaid is a jointly-funded, Federal-State health insurance program for certain low-income and needy people. It covers approximately 36 million individuals including children, the aged, blind, and/or disabled; and people who are eligible to receive federally assisted income maintenance payments.

access to patient charts, records, and discharge summaries. Direct reports are also more timely than manufacturer reports because there is no intervening processing time for submission of a report. According to FDA, timing is critical for the generation of early warning signals about previously unrecognized, serious ADRs.

Because physicians may not have time to complete and mail the MedWatch Form 3500 (Voluntary Reporting Form for Health Professionals) to FDA, we believe FDA should take stronger steps to encourage more direct ADR reporting by telephone. Our contention is based on the findings of a study of physicians' attitudes towards ADR reporting in Germany,¹⁵ which found that 65 percent of participants would be more willing to report ADRs by telephone. Although this relatively simple option is already available, FDA's MedWatch office receives less than 3 percent of reports of adverse reactions to FDA-regulated products by telephone. We believe that the interaction between skilled MedWatch personnel and reporting physicians could elicit important information concerning the patient's history and other data necessary to prepare a timely and useful ADR report. In discussing this option with FDA, cognizant officials stressed that a rise in telephone reporting would require an increase in personnel resources.

Pharmacist Reporting

According to FDA, pharmacists are also in a unique position to report high quality ADRs to the agency. The pharmacist has an in-depth knowledge of drugs, a close working relationship with other health care providers, and direct interactions with patients. In some circumstances, the pharmacist may be the first health care provider to be alerted to a possible ADR. In other situations, the pharmacist may be responsible for collecting, recording, and analyzing information provided by another health care provider. This may be particularly true in the hospital setting. During the period June 1, 1997 to May 31, 1998, America's approximately 190,000 pharmacists reported 7,406 ADRs directly to FDA. Again, FDA can do more to encourage a higher rate of pharmacists' reporting of ADRs--particularly by telephone.

Requiring Hospital Reporting of ADRs

Another method FDA could consider for enhancing the information it receives on ADRs is to tap into the information systems of the country's hospitals, which routinely collect information on ADRs. Both the American Medical Association and the Joint Commission on Accreditation of Health Care Organizations encourage hospitals to review and maintain ADR-related data. According to *Drug Topics* (January 4, 1998), more than 9 out of 10 hospitals are already involved in the review of ADRs. Thus, to capitalize on the information collected by hospitals, FDA could coordinate with HCFA to require hospitals to report all serious, unexpected ADRs to FDA as a condition for participation in Medicare and Medicaid. Currently, hospitals--over

¹⁵ *Pharmacoepidemiology and Drug Safety*, Vol. 7: Supplement 2: S79-S215 (1998).

6,000 of which participate in the Medicare and Medicaid programs--are not required by Federal authority to report ADRs to FDA.

Under HCFA's regulations at 42 C.F.R., Section 482.24(c), hospital medical records are required to have information on the patient's response to medications, and these records are supposed to document unfavorable reactions to drugs and anesthesia. Section 482.25(6) further requires that ADRs must be immediately reported to the attending physician, and, if appropriate, to the hospital's quality assurance program. Following from these regulations, HCFA's Intermediary Manual includes the requirement that any adverse drug reaction must be documented. The manual also requires that the patient's medical record contain specific data, including every dose of medication administered and any ADR.

Requiring hospitals to report serious, unexpected ADRs to FDA as a condition of Medicare and Medicaid could be set forth in regulations promulgated by the Secretary of HHS to implement her statutory authority to establish conditions under which hospitals may receive funding under the Medicare and Medicaid programs. We believe that such a requirement, which flows naturally from the current mandate to maintain ADR records, would not only assist the Department further in serving the interests of the health and safety of hospitalized patients, but also provide enhanced "intelligence" for FDA to more effectively carry out its mandate to monitor the safety of drugs.

Implementing Pro-Active Methods For Identifying ADRs

The FDA acknowledges that post-marketing surveillance is becoming an increasingly crucial component of drug safety assurance, and has recognized that its passive reporting system may not be adequate to provide such assurance. The agency has itself identified the need to move from a strictly passive ADR reporting process to one that is more pro-active in identifying ADRs.

One idea being considered by FDA¹⁶ is the creation of a network of sentinel sites, which involves using representative samples of user facilities to collect information based on epidemiological data and known relative risks. According to FDA, such a network would help provide optimal surveillance of products that are being used primarily at hospitals or clinics. The agency also believes representative facilities could maintain full and accurate reporting of a reasonably high proportion of all adverse events that occur for a given product. We encourage FDA to develop pro-active systems for identifying ADRs to supplement its existing passive reporting system.

¹⁶ The idea of sentinel reporting is cited in two FDA reports: "Initial Performance Plan Fiscal Year 2000 (June 1998)" and "Managing the Risks for Medical Product Use: Creating a Risk Management Framework" (May 1999).

Questions 6 and 7: How does FDA apply resources to the receipt, processing, and analysis of ADR reports; and are the agency's resources adequate?

In Fiscal Year (FY) 1999, FDA budgeted \$14.6 million, 69 full-time equivalents, and 109 full- and part-time contract personnel to handle the receipt, processing, and analysis of ADR reports. If the agency continues to conduct its ADR handling in the same manner as it has over the years, the current level of resources allocated is probably sufficient. However, as more drugs are approved for marketing, the agency will have to step up its monitoring responsibilities and more resources will likely be needed.

***CURRENT ALLOCATION
OF ADR RESOURCES***

The FDA maintains that its current allocation of personnel is adequate to “continue baseline support for CDER, including basic safety evaluation of incoming voluntary ADR reports, basic drug usage generation and review, basic follow-on study design and evaluation, and interaction with the review divisions for the most important regulatory action.”

The OPDRA has an authorized personnel ceiling of 69, with 57 actually on board as of April 1999. The FDA officials stated that when this authorized staffing level is achieved, the post-market surveillance program for drug safety will be re-evaluated using data generated over a period of time to estimate a more optimal level of service for the review divisions. The FDA officials also said that they are reviewing their current business processes and are designing new approaches for safety evaluation. These officials stated that they will ultimately make staffing estimates based on these exercises.

***RESOURCES MAY NEED TO BE
STRENGTHENED TO BE CONSISTENT
WITH INCREASED WORKLOAD
AND OTHER AGENCY EFFORTS***

While FDA believes the current allocation is sufficient for its current ADR operations, we believe that the agency needs to take into account the likely increase in its workload and the push for the agency to do more to protect the public from unsafe drugs on the market. According to data published by PhRMA, a substantial number of new drugs are under development, some for which new drug applications will be submitted to FDA in the next few years. Further, there is considerable interest among pharmaceutical professionals, academicians, the public, and the agency itself that FDA do more in the post-market surveillance area to ensure drug safety.

The FDA's Workload Will Likely Increase

The FDA's workload will likely increase due to the rising number of new drugs and new surveillance initiatives. The FDA, in making its resource allocation decisions, should consider the many new drugs currently under development for which applications may eventually be submitted to the agency for approval. When approved, these drugs will add to the approximately 10,000 prescription drugs already on the market and increase the workload of FDA personnel responsible for monitoring the safety of these drugs. According to PhRMA, the following drugs are in development: cancer - 354; infectious diseases - 136; neurologic disorders - 118; AIDS - 113; heart disease and stroke - 96; and mental illness - 85. The FDA has already approved 350 new drugs for marketing during the past 3 years (1996-1998), more than in any other 3-year period in the agency's history.

Within the group of drugs expected to be approved, FDA is anticipating a greater number of new molecular entities (NMEs)¹⁷ to be marketed in the U.S. Because the period of time following the marketing of an NME is when unexpected and serious adverse events come to light, FDA should expect to see more ADRs, particularly those that could lead to market withdrawal. Indeed, studies of ADR reporting generally show an increasing phase of reporting after the drug's launch followed by a plateau and then a more or less decreasing phase.¹⁸ Accordingly, FDA should ensure that it has sufficient staff on-board to evaluate the increased number of ADR reports generated by these drugs as they come on the market. If signals of serious, yet unrecognized drug-associated events are not promptly detected and regulatory action not taken in a timely manner, patients taking these drugs may be exposed to unacceptable risk resulting in disability, hospitalization, or even death.

Although FDA recognizes that it needs to improve its existing reporting systems and to build a sentinel surveillance system, the agency will likely need to identify additional resources for such initiatives. While we do not advocate any particular option to increase resources, we believe that resources could be obtained, for example, by: (1) re-allocating funds within FDA's existing budget parameters (that is, taking funds from other, less critical agency activities); (2) increasing FDA's annual budget appropriations; (3) expanding pre-market user fees to provide post-market coverage; or (4) instituting a user fee specifically focused on post-market drug surveillance. Within these possibilities, FDA could also explore expanding the use of contracts to augment its staffing and expertise in the post-market areas. In any case, the agency should take proactive measures to ensure that it is properly staffed and funded for upcoming post-market drug surveillance challenges.

¹⁷ The NMEs are chemically unique pharmaceuticals that have never before been marketed in the U.S. in any form.

¹⁸ *Pharmacoepidemiology and Drug Safety*, Vol. 7: Supplement 2: S79-S215 (1998).

Questions 8 and 9: Is FDA ensuring that manufacturers are complying with the Federal regulations to report ADRs to the agency; and what sanctions does FDA impose on manufacturers who do not comply with reporting requirements?

The FDA has increased the number of ADR inspections at manufacturer facilities, and, according to the agency's classification of these inspection reports, manufacturers appear to be in compliance with reporting requirements.

To ensure compliance with post-marketing ADR reporting requirements, FDA conducts on-site inspections of records at manufacturer facilities in accordance with agency enforcement regulations.¹⁹ For the 3-year period from FY 1996 to FY 1998, FDA completed 102 inspections as follows: FY 1996 - 17; FY 1997 - 33; and FY 1998 - 52. The FDA classified these inspection reports as follows: No Action Indicated - 62; Voluntary Action Indicated - 32; and Official Action Indicated - 8. No Action Indicated means that no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action). Voluntary Action Indicated means that objectionable conditions are found, but the FDA district is not prepared to take or recommend any administrative or regulatory action. The FDA district may advise the establishment following the inspection of findings that should be corrected, but the significance is not such to warrant warnings of administrative or regulatory actions or to request a response. Any corrective action is left to the establishment to take voluntarily. Official Action Indicated means that regulatory and/or administrative sanctions will be recommended. This includes voluntary recalls where the FDA district has decided conditions warrant either regulatory or administrative action.

***FEW WARNING LETTERS SENT
TO MANUFACTURERS***

Since 1989, FDA sent warning letters to three firms for non-compliance with ADR reporting requirements. A warning letter is a written communication from FDA notifying an individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug and Cosmetic Act, or other acts, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation, may result in administrative and/or regulatory enforcement action without further notice.

¹⁹ Compliance Program 8353.001, Chapter 53--Postmarketing Surveillance and Epidemiology: Human Drugs--Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations.

Question 10: What are the steps that can be taken to improve FDA's oversight and responses to ADRs?

Consistent with the consensus of professional opinion in the ADR arena, we believe FDA should take a more pro-active role in our nation's ADR system. Specifically, we recommend that the Commissioner of Food and Drugs:

1. Develop policies and procedures for more effective coordination between FDA post-market drug risk assessors and FDA's review divisions to better ensure that prompt and appropriate regulatory action is taken when necessary on those drugs identified in MARs.
2. Develop and implement a quality control system to ensure that signals of serious, yet unrecognized drug-associated adverse reactions that might indicate a public health problem are not overlooked.
3. Develop and apply methodologies to quantify the extent and scope of the ADR problem with the goal of reducing the occurrences of serious preventable ADRs.
4. Encourage greater interactive reporting of serious ADRs and product problems by health professionals directly to FDA by telephone to ensure that accurate and essential information necessary for regulatory action is received by the agency in a timely manner.
5. Coordinate with HCFA to require hospitals to report all serious, unexpected ADRs directly to FDA as a condition for participation in Medicare and Medicaid.
6. Explore pro-active methods to obtain ADR data to supplement the agency's passive post-marketing monitoring system.
7. Systematically evaluate the adequacy of post-marketing surveillance staffing levels necessary to effectively monitor the safety of the increasing number of marketed drugs and, as necessary, identify funding sources for additional staff.

AGENCY COMMENTS AND OIG RESPONSE

In its November 12, 1999 memorandum commenting on our draft report, dated August 4, 1999, FDA agreed with our recommendations and stated that it was taking or planned to take actions to strengthen the ADR reporting and handling process. The FDA provided editorial comments on the draft report along with its comments regarding our specific recommendations. Wherever possible, we incorporated the agency's editorial comments, and thus, to avoid confusion, have deleted the text of those comments from the appendix.

Below, we summarize the actions FDA has taken or plans to take regarding our specific recommendations:

1. Improving coordination between post-market risk assessors and FDA review divisions: The FDA stated that it has developed policies and procedures, now under review, addressing expectations and time frames for taking action on important safety signals and preparing MARs.
2. Ensuring signal detection through a quality control system: The FDA stated that it would use visualization tools such as CrossGraphs and “smart” tools such as the Bayesian data mining tool to provide a second level of ADR reporting.
3. Quantifying the extent of the ADR problem: The FDA stated that it would identify new statistical methods, establish action thresholds, and develop computer software to screen data bases to accurately identify signals of potential safety problems; and, with additional resources, improve its analysis of drug usage patterns.
4. Encouraging more interactive ADR reporting: The FDA stated that it would encourage greater interactive reporting of ADRs by extensive promotion of its toll-free telephone number.
5. Coordinating with HCFA to require hospital reporting of serious, unlabeled ADRs: The FDA stated that hospitals should report all serious, unexpected ADRs either directly or through the manufacturer. The agency believes that this issue should be further discussed with JCAHO since it has experience with the effects of mandatory reporting requirements on the quality of information received.
6. Exploring pro-active methods to obtain ADR data: The FDA stated that it has implemented, to a limited extent, a number of other, more pro-active risk assessment approaches including assessing large health care data bases, establishing product registries, and creating sentinel surveillance sites.
7. Evaluating the adequacy of post-market surveillance staff levels: The FDA stated that it has adjusted its resource allocation across program areas to provide additional staff to the post-marketing program and that additional resources for product safety have been requested through the appropriations process.

Although our recommendations were not directed at HCFA, we nevertheless wanted its reaction to our recommendation pertaining to hospitals reporting serious ADRs as a condition of participation in Medicare and Medicaid. In a November 15, 1999 memorandum regarding our recommendations, the Administrator of HCFA agreed that ADRs are serious health problems that need to be addressed, and stressed the need for a partnership among academicians, health professionals, enforcement agencies, and accreditation agencies to

educate care givers and share knowledge regarding ADR prevention. The Administrator also informed us that in the preamble to the final rule for the new hospital condition of participation, now being developed, the agency will emphasize the contribution ADR reporting makes toward the delivery of quality care and protection of public safety, and it will encourage the reporting of all ADRs to FDA.

APPENDIX



Memorandum

Date November 12, 1999

From Deputy Commissioner for Management and Systems

Subject FDA's Response to the OIG Draft Report, Review of the Food and Drug Administration's Handling of Adverse Drug Reaction Reports, A-15-98-50001

To June Gibbs Brown
Inspector General

Thank you for the opportunity to review and comment on the Office of the Inspector General's (OIG) Draft Report, *Review of the Food and Drug Administration's Handling of Adverse Drug Reaction Reports* (CIN A-15-98-50001). General and editorial comments are included, as well as, the Agency's response to the specific recommendations cited in the report. This supersedes my September 28, 1999 memorandum addressed to the Inspector General.

If you need additional information, please contact Paul Jones at (301) 827-4812.

Robert J. Byrd

Attachment

Recommendations of the OIG report:

1. **Develop policies and procedures for more effective coordination between FDA post-market risk assessors and FDA's review divisions to better ensure that prompt and appropriate regulatory action is taken when necessary on those drugs identified in MARs.**

We agree that the interactions between the review divisions and OPDRA need to be more effectively coordinated with appropriate documentation of policy and procedures. Ongoing policy discussions have taken place in the Office of Review Management regarding clarification and focus of reviewing functions and coordination on appropriate regulatory action. In conjunction with these discussions, a draft MaPP was created and is being reviewed. This MaPP addresses the expectations and timeframes for action on important safety signals identified by OPDRA such as MAR and will provide the basis for policy and procedures in this area.

In addition, there is an ongoing effort by the Office of Review Management to identify and clarify the appropriate area – new drug division or OPDRA – to take the lead on certain issues and to document and implement this authority. As a result, for some classes of drugs (such as pre-1938 drugs under 21 CFR 310 and nutritional supplements reclassified as drugs) primary safety assessment responsibility lies within OPDRA with the CDER Office of Compliance acting as the regulatory contact.

2. **Develop and implement a quality control system to ensure that signals of serious, yet unrecognized drug-associated adverse reactions that might indicate a public health problem are not overlooked.**

We agree that further enhancements are needed to ensure no important signals are overlooked by the post-marketing review system. In addition to increasing reviewer numbers (including Safety Evaluators and Epidemiologists), CDER is seeking contract and internal resources to move to the next phase of AERS development. This would include the use of visualization tools (commercial tools such as CrossGraphs) and eventually “smart” tools (such as the Bayesian datamining tool under development) to provide a second level of review for incoming reports.

The Agency has recently established relationships and communications with our worldwide sister regulatory bodies. For example, we've established regular videoconferences with Health Canada and EMEA to facilitate discussion of signals and other postmarketing safety concerns. At these videoconferences, safety signals and risk management strategies are discussed. These efforts directly address the concerns expressed in the OIG report that we are not overlooking potential safety problems.

Additional quality control steps will include periodic safety reviews independent of individual ICSR review and a systematic review of the firm's PSUR document that will provide another level of insight into completeness and accuracy of event reporting.

Other quality control measures in the OPDRA review system are also being explored, including improved quality assurance at the input level, quality control steps for electronic entry, and additional process steps at the independent Safety Evaluator level.

3. Develop and apply methodologies to quantify the extent and scope of the ADR problem with the goal of reducing the occurrences of serious preventable ADRs.

We agree that the extent and scope of the ADR problem needs to be better understood. FDA has put some effort into developing improved tools to explore spontaneous reporting databases so potential problems can be identified. Such efforts include identifying new statistical methods, establishing action thresholds, and developing computer software to screen databases to accurately identify signals of potential safety problems. Resources permitting, FDA would expand its pharmacoepidemiological and methodological research both to identify signals and to perform follow-up investigations of potential safety problems. Additional resources in this area would allow improved ascertainment of drug usage patterns. Understanding by whom and how a drug is being used is essential to anticipating safety issues as well as interpreting safety signals that are generated through spontaneous reporting. Another critical element is improved understanding and quantification of background rates for outcome events. For example, getting a more precise quantification of the incidence of aplastic anemia in a given patient population is absolutely critical for interpreting the reporting rates generated from spontaneous reports received by the Agency.

4. Encourage greater interactive reporting of serious ADRs and product problems by health professionals directly to FDA by telephone to ensure that accurate and essential information necessary for regulatory action is received by the Agency in a timely manner.

We agree that greater interactive reporting of serious ADRs should be encouraged. The vast majority of manufacturers' reports originate from health care providers; we believe the bulk is initiated by phone. Manufacturers also use phone interviews to obtain additional information on reported events.

While we do not believe reports should be diverted from the manufacturer to the FDA, we strongly encourage health professionals not reporting directly to manufacturers to report to the Agency. Through MedWatch, healthcare professionals and consumers are encouraged to report serious adverse events and product problems to the FDA, the manufacturer, or both. MedWatch has

established a toll-free number to receive reports by telephone and extensive promotion of the phone-in option will continue.

5. **Coordinate with the Health Care Financing Administration (HCFA) to require hospitals to report all serious, unexpected ADRs directly to FDA as a condition for participation in Medicare and Medicaid.**

We agree that hospitals should report all serious, unexpected ADRs to the Agency. This could be accomplished via reporting through the manufacturers or directly to the FDA. Limiting mandatory reporting to the FDA to those ADRs that are serious and unexpected is critical because, without significant additional resources, we do not have the manpower to investigate and triage all ADRs.

We believe this issue should be further discussed with the Joint Commission on Accreditation of Health Organizations (JCAHO) as they have long-standing experience with the effects of mandatory reporting requirements on the quality of information received.

6. **Explore pro-active methods to obtain ADR data to supplement the Agency's passive post-marketing monitoring system.**

We concur with this recommendation. In the area of postmarketing risk management, CDER's emphasis is on passive, spontaneous reporting (through AERS), designed to detect rare, unanticipated adverse events. However, the Agency has implemented, to a limited extent, a number of other, more proactive risk assessment approaches, including accessing large healthcare databases, establishing product registries, and creating sentinel surveillance sites. We agree with the OIG recommendation that these approaches should be further explored and expanded to enhance our ability to rapidly identify, quantify, and understand the risks associated with the use of medical products, but current resources do not support enhancing these approaches.

7. **Systematically evaluate the adequacy of post-marketing surveillance staffing levels necessary to effectively monitor the safety of the increasing number of marketed drugs and, as necessary, identify funding sources for additional staff.**

We agree that staffing levels for post-marketing surveillance should be routinely evaluated and adjusted as needed to assure continued safety of marketed products. Additional resources for product safety have been requested through the federal budget appropriations process. In addition, over the past several years, CDER has internally adjusted our resource allocation across program areas to provide additional staff to the post-marketing program.