Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

HOSPITAL REPORTING OF ADVERSE DRUG REACTIONS

Richard P. Kusserow
INSPECTOR GENERAL

JULY 1991

OFFICE OF INSPECTOR GENERAL

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Department of Health and Human Services

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OEI-12-90-01000

EXECUTIVE SUMMARY

PURPOSE

The purpose of this study is to: (1) determine the extent to which hospital pharmacists are familiar with the Food and Drug Administration's Spontaneous Reporting System (SRS) for reporting adverse drug reactions (ADRs); (2) determine the nature and frequency of hospitals' in-house ADR monitoring; and (3) identify any reasons why hospitals do not report ADRs to the FDA.

BACKGROUND

While extensive testing is conducted on all prescription drugs prior to marketing approval from FDA, not all adverse reactions are detected at this time, as some are extremely rare or occur only in special populations. Consequently, it is only after the wider use that occurs after the drug is marketed, which may include unapproved uses and different patient populations, that some ADRs are detected. FDA collects adverse drug reaction reports from pharmaceutical manufacturers, medical professionals, postmarketing studies and the medical literature. Pharmaceutical manufacturers are required to report all ADRs, while reporting from medical professionals is voluntary.

FDA undertakes many activities to encourage reporting by medical professionals, including pilot projects to increase physician reporting of ADRs and a task force to study hospital reporting. This report provides additional information about in-house ADR reporting programs in hospitals and hospital reporting of ADRs to FDA.

METHODOLOGY

Data for this survey were gathered by conducting a mail survey of 1260 hospital pharmacy departments randomly selected from the American Hospital Association's listing of hospitals in the U.S. and stratified by size. Additionally, we conducted a literature review concentrating on reports of hospital ADR programs appearing in the medical literature. Finally, we conducted interviews with the Joint Commission on Accreditation of Healthcare Organizations and the American Society of Hospital Pharmacists to obtain their views on hospital reporting of ADRs.

FINDINGS

I. Ninety-two percent of all hospitals know how to report adverse drug reactions (ADRs) to the FDA. However, 14 percent of small hospitals are unaware of the proper reporting procedure.

Overall, knowledge of how to report adverse reactions to FDA is quite high with less than ten percent unaware of FDA's system and how to use it. However, a significant difference exists in the awareness level among hospitals of different sizes, with small hospitals much less likely to be aware of FDA's reporting process.

II. Respondent hospitals are engaged in several aspects of ADR reporting; some activities are more commonly performed in medium and large hospitals.

Our survey respondents indicated that their hospitals are conducting several activities as part of in-house ADR monitoring and reporting programs. These activities include collection of patient information at the time of the adverse event, routine screening of patient medical records, and training for hospital staff in how to detect and report ADRs.

III. There are several factors affecting hospital reporting of ADRs to FDA.

A total of 51 percent of our respondent hospitals indicate that they reported no adverse drug reactions to FDA in 1989. This response was more common among the small hospitals (68 percent) than the medium and large hospitals (42 and 29 percent, respectively). Regardless of the accuracy of these numbers, it would appear that there are factors affecting ADR reporting to FDA by hospitals.

A. Hospitals indicate that they hesitate to report ADRs to the FDA when they are unsure that the drug caused the reaction.

B. Fifty-seven percent of hospitals have policies in place requiring approval by an additional hospital committee or department before an ADR is reported to FDA.

RECOMMENDATIONS

I. To improve hospital reporting of adverse drug reactions, FDA should clarify for hospitals the role of causality assessment when reporting adverse drug reactions to FDA.

II. FDA should evaluate the role of physicians in hospital reporting of adverse drug reactions.

III. FDA should sponsor pilot studies to further study reasons why hospitals hesitate to report ADRs to FDA and develop methods to encourage ADR reporting by hospitals.

AGENCY COMMENTS

Within the Department of Health and Human Services, the Public Health Service (PHS) provided comments to this report. The PHS concurred with our recommendations and were generally favorable about the report.

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INTRODUCTION

PURPOSE

The purpose of this study is to: (1) determine the extent to which hospital pharmacists are familiar with the Food and Drug Administration's Spontaneous Reporting System (SRS) for reporting adverse drug reactions (ADRs); (2) determine the nature and frequency of hospitals' in-house ADR monitoring; and (3) identify any reasons why hospitals do not report ADRs to the Food and Drug Administration.

BACKGROUND

The Food and Drug Administration (FDA) defines an adverse drug reaction as the following:

> *"An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."* (21 CFR part 201)

While extensive testing is conducted on all prescription drugs prior to marketing approval from FDA, not all adverse reactions are detected at this time, as some are extremely rare or occur only in special populations. Consequently, it is only after the wider use that occurs after the drug is marketed, which may include unapproved uses and different patient populations, that some ADRs are detected. To acknowledge this situation and capture important additional information available after a drug's approval, FDA established the Spontaneous Reporting System. The SRS acts primarily as an early warning system indicating a potential relationship between an adverse reaction and a given drug. FDA may then determine if additional studies are needed to confirm the adverse reaction. Eventually the information received through the SRS may be used to revise product labeling and alert medical professionals of new serious reactions.

FDA receives the majority of ADR reports from pharmaceutical manufacturers, medical professionals, and to a lesser extent from postmarketing clinical trials and the medical literature. Pharmaceutical manufacturers are required to submit periodic ADR reports quarterly during the first three years of marketing a drug and annually thereafter. Reports of serious adverse reactions not listed in the drug's labeling must be submitted within 15 days, as well as increases in the frequency of labeled serious adverse reactions. FDA defines a serious ADR as one resulting in death, hospitalization, disability, congenital abnormality, or cancer.

Although voluntary, direct physician reporting of adverse drug reactions has been shown to be an important contribution to FDA's postmarketing safety data. In a study conducted by Rossi and Knapp, reporting by physicians and other medical professionals was shown to result in a higher proportion of labeling changes based on the number of reports filed in comparison to reports from pharmaceutical manufacturers.[1] Direct reporting also allows FDA to contact the medical professional for additional information if necessary.

FDA encourages direct reporting by medical professionals through a variety of programs, reminders, and educational materials. To encourage physician involvement, reporting forms are mailed to all practicing physicians several times a year. Additionally, FDA has sponsored pilot projects through several State health departments in an effort to increase community-based physician reporting of ADRs. The Rhode Island project has included a mail survey to identify barriers to physician reporting and the distribution of ADR reporting kits combined with educational sessions to encourage FDA reporting.[2] FDA has also undertaken activities encouraging reporting by hospital pharmacists, including informational kits for hospitals developing an ADR system and articles in major professional journals. Also, FDA has formed a task force composed of representatives from several major hospitals to formulate guidelines for a model hospital ADR program.

Additionally, new requirements have been established by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). As a condition of accreditation, hospitals must have in place or develop an in-house monitoring and reporting program for ADRs. The primary objectives of these in-house hospital programs are primarily improved quality assurance and risk management so that optimal drug therapy is delivered to all patients. Additionally, these programs can provide valuable information concerning new adverse drug reactions. Adverse reactions of this type are of the greatest interest to FDA, since many of the adverse reactions that hospitals will collect information on are already known.

In light of FDA interest and the new JCAHO requirements hospital reporting of ADRs is worthy of additional attention. This study provides basic information about hospital ADR monitoring and reporting activities.

METHODOLOGY

Data were gathered from the following sources for this study.

First, to determine awareness and usage of FDA's ADR reporting system and in-house policies and procedures among hospitals, we conducted a mail survey of 1260 hospital pharmacy departments. Hospitals were selected randomly from the American Hospital Association's listing of hospitals in the U.S. and stratified by size to ensure appropriate representation of small (less than 100 beds), medium (100 to 499 beds), and large (500 or more beds) hospitals. Large hospitals were oversampled at the request of FDA, because they have traditionally represented the greatest percentage of ADR reports from hospitals overall. We received a total of 826 usable surveys, resulting in an overall response rate of 66 percent. The survey results in this report are primarily presented by strata and are not projected to the universe of all hospitals in the U.S., since non-respondent hospitals in the stratum of small hospitals differed from our respondents. (Additional details regarding respondents, stratification, weighting and response rates are provided in Appendix A).

Second, to obtain additional information concerning hospital ADR programs, we conducted a literature review concentrating on reports of hospital ADR systems appearing in the medical

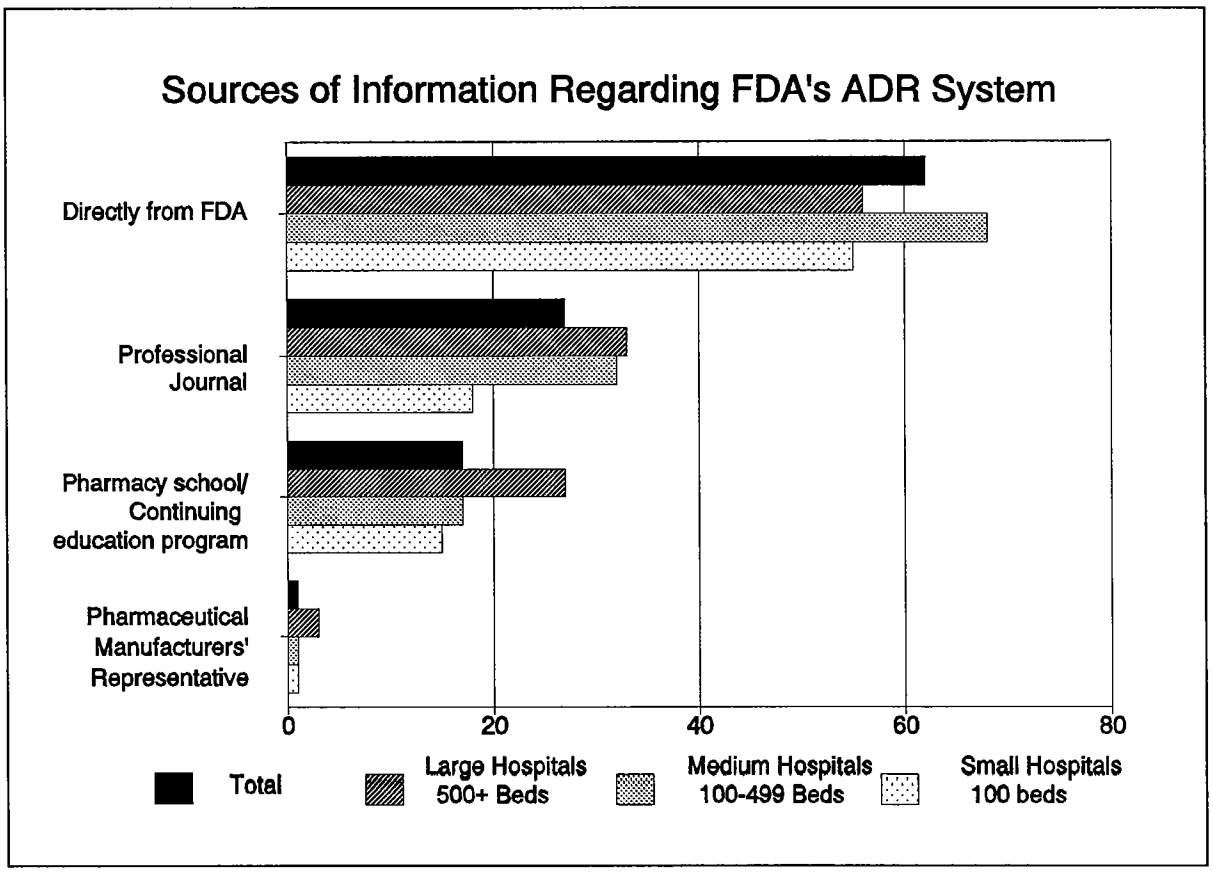
literature. Third we conducted interviews with the Joint Commission on Accreditation of Healthcare Organizations and the American Society of Hospital Pharmacists to obtain their views on hospital reporting of ADRs.

FINDINGS

I. ***Ninety-two percent of respondent hospitals know how to report adverse drug reactions (ADRs) to the FDA. However, 14 percent of small hospitals are unaware of the proper reporting procedure.***

Overall, knowledge of how to report adverse reactions to FDA is quite high with less than ten percent unaware of FDA's system and how to use it. However, a significant difference exists in the awareness level among hospitals of different sizes. Only 85 percent* of small hospitals [95% confidence interval (C.I.), 0.799 to 0.894] are aware of FDA reporting procedures compared to 96 and 98 percent of medium and large hospitals (95% C.I., 0.931 to 0.978; and 0.957 to 0.992), respectively.

The majority of hospitals (62 percent) receive information on FDA's ADR system directly from FDA. Other important information sources for hospitals about FDA's ADR system are professional journals and professional and continuing education. Professional journals are most important as informational sources to large and medium sized hospitals. Similarly, educational programs are significant primarily to large hospitals. Among respondents of all sizes, pharmaceutical manufacturers' representatives are not a significant source of information on how to report ADRs to FDA.



* One percent of small hospitals did not respond to this question.

II. *Respondent hospitals are engaged in several aspects of ADR reporting; some activities are more commonly performed in medium and large hospitals.*

Our survey respondents indicated that their hospitals are conducting several activities as part of in-house ADR monitoring and reporting programs. These activities include collection of patient information at the time of the adverse event, routine screening of patient medical records, and training for hospital staff in how to detect and report ADRs. A total of 91 percent of the respondent hospitals have some type of data collection form for reporting ADRs. Among respondents, large hospitals (99 percent; 95% C.I., 0.975 to 0.997) are more likely to have forms for collecting ADR information, than medium (94 percent; 95% C.I., 0.910 to 0.966) or small (85 percent; 95% C.I.,0.800 to 0.896). Seventy percent of the respondent hospitals use customized forms developed within the hospital for collecting ADR information.

Slightly less than one-half of the respondents (47 percent) indicated that in their hospital patient medical records are routinely screened for signs of ADRs. Screening for adverse drug reactions may include periodically reviewing the patient's chart, screening medication orders as they are received in the pharmacy, and screening laboratory data.[3]

Slightly greater than one-half of all the respondents offer some type of periodic training or education for staff on how to detect and report ADRs. A greater percentage of large and medium hospitals (60 and 59 percent, respectively; 95% C.I. 0.553 to 0.660 and 0.535 and 0.648) offer periodic training for hospital staff in detecting and reporting ADRs compared to small hospitals (40 percent; 95% C.I., 0.331 to 0.461). Training methods used by hospitals range from traditional in-service lectures to innovative videotape presentations developed within the hospital.[4]

III. *There are several factors affecting hospital reporting of ADRs to FDA.*

A total of 51 percent of our respondent hospitals indicated that they reported no adverse drug reactions to FDA in 1989. This response was more common among the small hospitals (68 percent; 95% C.I., 0.615 to 0.740) than the medium and large hospitals (42 and 29 percent, respectively; 95% C.I., 0.365 to 0.479 and 0.238 to 0.337). Regardless of the accuracy of these numbers, it would appear that there are factors limiting ADR reporting to FDA by hospitals (greater detail of this statistic is provided in the Appendix).

A. *Hospitals indicate that they hesitate to report ADRs to the FDA when they are unsure that the drug caused the reaction.*

Fifty-one percent of hospitals hesitate to report ADRs to the FDA because they are uncertain whether the suspected drug actually caused the adverse reaction. This hesitation is of particular interest in light of the fact that FDA does not require positive proof of causality as a condition to report an ADR. In fact, a single report is generally insufficient to determine a definite cause and effect relationship between a drug and a given adverse event.

Despite this, a majority of hospitals (74 percent) conduct follow-up to assess the likelihood of causality for at least all serious reactions. To assess causality, hospitals may use several methods including discontinuing and rechallenging with the suspected drug, application of one of several algorithms*, and evidence of similar reactions in the medical literature. Although discontinuing and rechallenging with the suspected drug is perhaps most useful, it may not be practical for particularly severe reactions. Fifteen percent of hospitals responding to our survey rechallenge with the suspected drug to determine causality. Use of algorithms solely is more common in large hospitals (22 percent; 95% C.I., 0.176 to 0.267) as opposed to medium (13 percent; 95% C.I., 0.086 to 0.163) and small hospitals (4 percent; 95% C.I., 0.015 to 0.068).

(*An algorithm is a formula which assigns numeric values to aspects of the adverse event which are used to predict the probability of a causal relationship with the suspected drug.)

Appropriately, 66 percent of hospitals hesitate to report to FDA when the adverse reaction is expected or not severe. This is consistent with the greater emphasis FDA places on the reporting of new serious reactions. If all hospitals were to report all of their observed ADRs, FDA would be overwhelmed with numerous reports with little significance. Other reasons hospitals mention for hesitating to report to the FDA include lack of time (11 percent), reporting to the manufacturer considered sufficient (8 percent), concern over legal liability (6 percent), lack of forms (5 percent), and not knowing how to report (4 percent).

Reasons for Hesitating to Report ADRs to FDA

	Percentage of Respondents			
Reasons for not Reporting	**Total**	**Small (<100) Hospitals**	**Medium (100 - 499) Hospitals**	**Large (500+) Hospitals**
Reaction was expected/not severe	66	59	69	72
Unsure that drug caused the reaction	51	50	52	51
Do not have the time	11	11	11	8
Consider reporting to manufacturer sufficient	8	9	8	8
Concern over legal liability	6	3	8	5
Do not have forms (FDA form 1639)	5	7	3	2
	Not addititive*	Not additive*	Not additive*	Not additive*

**Respondents gave one or more reasons*

B. *Fifty-seven percent of hospitals have policies in place requiring approval by an additional hospital committee or department before an ADR is reported to FDA.*

In many hospitals the pharmacy department may not have the authority to report ADRs to the FDA without approval or concurrence from the physician, committees, or other departments within the hospital. The most frequently mentioned entity involved in ADR reporting is the Pharmacy and Therapeutics (P & T) committee. This committee, which often has a majority of physician members, is involved in the decision to report an ADR to FDA in 42 percent of hospitals. Similarly, concurrence or approval by the prescribing physician is necessary in 25 percent of hospitals. Other committees that are involved less frequently in the decision to report an ADR to FDA include Quality Assurance (13 percent) and Risk Management (9 percent). Hospitals operated by the Veterans Administration (VA) are required to send reports of ADRs to the VA Central Office, instead of directly to FDA.

Required Approval/Concurrence to Report an ADR to FDA

	Percentage of Respondents			
Type of Approval/Concurrence	Total	**Small (<100) Hospitals**	**Medium (100 - 499) Hospitals**	**Large (500+) Hospitals**
Pharmacy & Therapeutics committee	42	40	44	48
Attending/Prescribing Physician	25	29	21	25
Quality Assurance committee	13	16	11	8
Risk Management	9	10	9	5
No approval/concurrence required	43	46	43	35
	Not addititive*	Not additive*	Not additive*	Not additive*

**Respondents gave one or more reasons*

In hospitals where approval is required by the prescribing physician or physician dominated committees, such as the P & T committee, ADR reporting to FDA may be subject to some of the barriers of physician reporting. For example, while our respondents themselves did not rate liability concerns as a reason for not reporting to the FDA, several did note that it is a significant concern among physicians. Additionally, a few respondents commented that required approval or concurrence from Pharmacy and Therapeutics or Quality Assurance Committees to report to FDA can be quite difficult to obtain. One respondent indicated that in his hospital the Risk Management Committee becomes anxious if ADRs are identified in patient discharge summaries.

RECOMMENDATIONS

I. ***To improve hospital reporting of adverse drug reactions, FDA should clarify for hospitals the role of causality assessment when reporting adverse drug reactions to FDA.***

The most important action FDA can take to improve ADR reporting from hospitals is to clarify the role of causality assessment. Uncertainty over whether the drug caused the adverse reaction is the most significant reason why hospitals say they hesitate to report ADRs to FDA. Also, the majority of medium and large hospitals regularly conduct follow up to assess causality for serious adverse reactions. Given the difficulty of establishing a cause and effect relationship on the basis of one observed adverse reaction, there is a great probability that hospitals are not filing reports that would be of use to FDA when analyzed collectively. FDA should develop some method to directly communicate with hospitals the need to report adverse reactions even when definite causality cannot be determined.

II. ***FDA should evaluate the role of physicians in hospital reporting of adverse drug reactions.***

Physicians and physician committees are involved in ADR reporting in a significant percentage of the respondent hospitals. While the full impact of their involvement cannot be quantified, it is probable that physicians are in some way influencing ADR reporting. Any efforts undertaken by FDA to further encourage hospital reporting of ADRs should take physicians into consideration. Efforts targeted solely at hospital pharmacists may not result in increased reporting to FDA if physicians involvement is not taken into account.

III. ***FDA should sponsor pilot studies to further study reasons why hospitals hesitate to report ADRs to FDA and develop methods to encourage ADR reporting by hospitals.***

FDA should take advantage of the current climate of interest in ADR monitoring and reporting that exists as a result of the new requirement from the Joint Commission on Accreditation of Healthcare Organizations that all hospitals develop in-house ADR programs. This period of heightened awareness offers an excellent opportunity to further explore the reasons why hospitals hesitate to report ADRs to FDA and to find successful ways to encourage reporting. Hospitals vary in their approaches to setting up these programs so that ADR monitoring and reporting are successfully carried out. Pilot programs would offer FDA the opportunity to examine hospital programs in greater detail and to determine what activities might be undertaken to increase reporting to FDA.

AGENCY COMMENTS

Within the Department of Health and Human Services, the Public Heath Service (PHS) provided comments to this report. The PHS concurred with our recommendations and were generally favorable about the report. A detailed copy of the comments are provided in Appendix B.

NOTES

1. Rossi, A.C. and Knapp, D.E. Discovery of new adversy drug reactionis: A review of the Food and Drug Administration's spontaneous reporting system. *JAMA* 252:1030-1033, 1984.

2. Scott, H.D. et al. Rhode Island physicians' recognition and reporting of adverse drug reactions: Increased physician's participation in post-marketing surveillance will lead to greater understanding of adverse drug reactions. *Rhode Island Medical Journal* 70:311-316, 1987.

3. Berry, L.L. et al. Sensitivity and specificity of three methods of detecting adverse drug reactions. *Am J Hosp Pharm* 45:1534-1539, July 1988.

4. Morgan, S.A. and Frank, J.T. Development of a videotape on adverse drug reactions. *Am J Hosp Pharm* 47:1340-1342, June 1990.

APPENDIX A

Methodological Approach

The objective of this study was to determine the level of awareness of FDA's adverse drug reaction reporting system among hospitals and to profile in-house ADR reporting activities in hospitals. Surveys were mailed to the Directors of Pharmacy Services for each of the hospitals in the sample. Directions were given for the survey to be completed by the Director or some other appropriate designee (profile of respondents may be found in Table A). No attempt was made to eliminate Federal or military hospials from the sample, as these hospitals are also potential sources of ADR reports for FDA.

Design Specifications and Sample Selection

The sample was randomly selected from the 1987 American Hospital Association's (AHA) listing of hospitals in the U.S. The sample was stratified by size (defined as the number of licensed beds according to AHA) into three groups: small (less than 100 beds), medium (100 to 499 beds), and large (500 beds and over). An equal sample was drawn for each strata, resulting in an oversampling for the stratum of large hospitals due to the smaller universe of large hospitals.

A size of approximately 1260 hospitals assumed a 40 percent response rate and a 95 percent confidence interval that would be within 5 percent of the true reporting rate, with the hypothesized reporting rate assumed to be 10 percent for the small and medium strata and 20 percent for the large stratum. In fact, we achieved a higher response rate and a higher rate of reporting among the respondents. The precision of our results are therefore well within the parameters of the design.

Eight weeks after the mailing date, 826 surveys had been returned to our office. This represents a total response rate of 66 percent. The following table displays the response rate by individual strata.

Response Rate by Hospital Size

Hospital Size (by number of beds)	N	Response Rate
Small (<100)	217	52%
Medium (100-499)	289	69%
Large (500+)	320	76%
Total	826	66%

Non-Respondent Analysis

An important consideration in surveys such as this type is the bias that may be introduced into the results if the non-respondents are different than those that responded to the survey. To determine the presence of any bias, we contacted by telephone a minimum of ten hospitals per strata selected in the original sample that did not complete a survey. These non-respondent hospitals were asked the following key questions from the survey: (1) Are you aware of how to report an ADR to the FDA? (2) Did you report any ADRs to FDA during calendar year 1989? Finally, nonrespondents were asked why they chose not to participate in the survey.

Among medium and large hospitals answers did not differ from those of the respondent hospitals. Nonrespondent small hospitals, however, differed significantly from those participating in our survey. Approximately one-half of the nonrespondent hospitals in the small category did not have pharmacy departments. In these hospitals, we were unable to locate an individual with knowledge of or responsibility for ADR reporting. As our results may be optimistic in the stratum of small hospitals we have chosen not to project our results to the universe of all hospitals in the U.S.

Projected Number of ADRs

In the survey hospitals were asked to indicate the approximate number of ADRs they reported to FDA during the calendar year 1989. Respondents provided this information by checking the appropriate range of numbers for the reports they sent in. In the table below is a projection, based on a representative number for each range, of the total number of ADRs the respondent hospitals should have reported to FDA in 1989. These numbers were then weighted to the universe of each stratum to provide an estimation of the reporting from all hospitals in the U.S. It is interesting to note from this calculation that while large hospitals are providing the greatest number of reports per hospital, it appears that reports from medium hospitals may be constituting the largest percentage of the reporting activity.

Projected Number of ADRs Reported to FDA in 1989

	Number of Respondent Mentions			Total Projected Number[1] of ADRs Reported to FDA		
Number of ADR Reports Respondents sent to FDA in 1989	**Small (<100) Hospitals**	**Medium (100-499) Hospitals**	**Large (500+) Hospitals**	**Small (<100) Hospitals**	**Medium (100-499) Hospitals**	**Large (500+) Hospitals**
0	147	122	92	0	0	0
1-5	61	127	133	152.5	317.5	332.5
6-10	3	21	37	22.5	157.5	277.5
11-20	1	8	22	15	120	330
>20	1	7	33	20	140	660
Total (excluding No Answer)	213	285	317	210	735	1600
				(8%)	(29%)	(63%)
Total Projected Number[2] of ADRs Reported to FDA by all Hospitals				**1629 (18%)**	**5768 (63%)**	**1897 (20%)**

[1] *Calculated by using the midpoint of each interval, except for the >20 category, where a value of 20 was used.*

[2] *Calculated by weighting the estimated number to the universe of hospitals by strata, as provided below:*

	Small	Medium	Large
Universe	3258	3296	498
Sampled	420	420	420
Weight	7.7571	7.8476	1.1857

TABLE A
Respondent Demographics

Survey Participant Job Title	Percentage (n=826)
Pharmacy Director, Associate, Assistant	76
Clinical Pharmacist (drug information)	8
Clinical Pharmacist (general)	6
Pharmacist Supervisor	6
Staff Pharmacist	2
Other*	1

**includes Hospital Administrators and Nurses*

Teaching Affiliation	Percentage (n=826)
University Affiliated/Research	15
Community/Teaching	23
Community/Non-teaching	52
Veterans Administration/Military	9
No Answer	2

Financial Affiliation	Percentage (n=826)
For Profit	14
Not for Profit/Charity	51
County-operated	14
State-operated	10
Federally-operated	11

APPENDIX B

Detailed Comments on the Draft Report

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

JUL 15 1991

Date

From Assistant Secretary for Health

Subject PHS Comments on OIG Draft Report "Hospital Reporting of Adverse Drug Reactions," OEI-12-90-01000

To Inspector General, OS

Attached are the PHS comments on the subject draft report. We concur with each of the recommendations and have taken or plan to take actions to implement them.

James O. Mason

James O. Mason, M.D., Dr.P.H.

Attachment

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IG	✓
PDIG	✓
DIG-AS	✓
DIG-EI	✓
DIG-OI	✓
AIG-MP	
OGC/IG	✓
EX SEC	
DATE SENT	7/17

COMMENTS OF THE PUBLIC HEALTH SERVICE ON THE OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT, "HOSPITAL REPORTING OF ADVERSE DRUG REACTIONS," OEI-12-90-01000, MAY 1991

General Comments

We found the OIG draft report informative and useful. Although the report shows that knowledge of how to report adverse drug experiences (ADE) to the Food and Drug Administration (FDA) is quite high, FDA's Center for Drug Evaluation and Research (CDER) will continue to work for greater understanding and use of the FDA system by all health care providers. Over the past several years, CDER's efforts to improve all aspects of the system have led to a significant increase in the annual number of reports submitted--increasing from 38,854 in 1985 to 75,230 in 1990. CDER is committed to continue its efforts in this area.

We share the OIG's concerns about the importance of hospital ADE reporting. Hospital based health care workers make a significant contribution to the FDA's Spontaneous Reporting System, both through direct reports to FDA and reports submitted to manufacturers and then forwarded to FDA. CDER will continue its efforts to assure that physicians and other hospital providers are knowledgeable about the procedure for ADE reporting and continue to encourage them to report suspected ADEs without regard to causality assessment.

This OIG report refers to episodes of adverse reactions as adverse drug reactions (ADR). Within FDA, these are known as adverse drug experiences (ADE). The PHS comments follow FDA's nomenclature.

OIG Recommendation

1. To improve hospital reporting of adverse drug reactions, FDA should clarify for hospitals the role of causality assessments when reporting adverse drug reactions to FDA.

PHS Comment

We concur. CDER has already taken a number of steps to clarify and promote its ADE reporting requirements to manufacturers and health care providers.

In 1985 (amended in 1987), FDA clarified its ADE reporting requirements as they relate to manufacturers (21 CFR 314.80 and 21 CFR 310.305). These regulations require manufacturer reporting irrespective of any causality assessment and state:

> "A report or information submitted by an applicant under this section (and any release by FDA that the report of information) does not necessarily reflect a conclusion by the applicant or FDA that the report

> or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect" (21 CFR 314.80 (1)).

FDA has also encouraged health providers to report adverse experiences to the Agency if there is a "suspicion" that the drug is related to the adverse experience. The Agency has discouraged causality assessment as a prerequisite for ADE reporting in an effort to be inclusive rather than exclusive.

In writing about reporting adverse experiences to FDA, non-FDA sources have also helped educate health providers to report suspected adverse reactions and have emphasized that a causality assessment is not needed for reporting.

When hospitals request information on adverse experience reporting, CDER's Office of Epidemiology and Biostatistics routinely sends a packet of information. This packet of information was recently updated and specifically states:

> "Please note that FDA is interested in all such events <u>associated</u> with a drug. Thus, causality need <u>not</u> be established before deciding to report an adverse drug reaction to FDA."

In summary, CDER will continue to explain FDA's position on causality which is that the suspicion of a relationship between a drug and an adverse experience is enough to initiate reporting. No causality assessment is required.

<u>OIG Recommendation</u>

2. FDA should evaluate the role of physicians in hospital reporting of adverse drug reactions.

<u>PHS Comment</u>

We concur. FDA plans to continue its efforts in this area. For some time, FDA has been concerned about physician ADE reporting. For example, in an effort to understand physician behavior in reporting ADE and to assess ways to improve direct reporting of ADEs, FDA initiated a contract research program through State health departments in 1985. Maryland and Rhode Island were awarded the first two pilot test contracts to survey physicians' existing attitudes and to design interventions to promote and increase ADE reporting.

To investigate the feasibility of increasing ADE reporting within hospitals, a third pilot contract was awarded to Mississippi in 1986. In 1987, Massachusetts and Colorado were awarded contracts to use and build on the interventions developed by the first three States. The program has been successful in stimulating the reporting of ADEs by physicians. Further, FDA staff have given numerous presentations and written a number of papers on physicians' ADE reporting.

Though we have long encouraged physician ADE reporting, we also recognize that hospital reporting is very complex with many hospitals having several pharmacies and satellites, many physicians and other health care providers and an intricate infrastructure of departments and committees. Additionally, most hospitalized patients are on more than one drug and any ADE can be confounded by these drugs, disease and other factors. Nonetheless, we maintain that hospital reporting strategies should not be limited to any professional group. FDA continues to encourage reporting from all health professionals.

OIG Recommendation

3. FDA should sponsor pilot studies to further study reasons why hospitals hesitate to report ADRs to FDA and develop methods to encourage ADR reporting by hospitals.

PHS Comment

We concur in principle with the need for further study and promotion but believe it should be incorporated within FDA's current efforts rather than a separate effort.

FDA's CDER shares the interest in learning more about reporting patterns and practices and has a number of targeted ongoing activities which it believes will achieve this purpose. CDER is continuing to learn about ADE reporting practices and patterns from the Epidemiologic Cooperative Agreements, State Contracts, and other activities.

The current ADE reporting contracts with the State Health Departments in Mississippi, Rhode Island and Colorado indicate the requirement for continual conduct of educational and promotional interventions geared toward increasing the quantity and quality of ADE reports coming from hospitals. Workshops such as the June 1989 Rhode Island Workshop on ADE Monitoring in Hospitals have been held by all of the contractors. These seminars include information on FDA's goals and objectives for ADE monitoring.

Two new cooperative agreements were awarded in May and June 1991 that relate to ADE monitoring and reporting systems. The first is based on a national network of clinical pharmacists that seeks to harness the adverse drug event monitoring activities required of hospitals by the Joint Commission on Accreditation of Healthcare Organizations to create a systematic mechanism for collecting comprehensive data on ADEs. The second proposes to initiate routine safety surveillance of newly marketed drugs by establishing a signal detection system in a large health maintenance organization.

In summary, we believe that FDA's efforts fully satisfy the intent of the OIG recommendation.

Technical Comments

1. Executive Summary, Background, Fourth Line

   The report uses the word "untested" to inaccurately describe unapproved uses of marketed drugs. In order to convey a more accurate meaning, we recommend that the word "unapproved" be substituted for the word "untested."

2. Introduction, Background, Second Paragraph, Fourth Line

   Same as number 1 above.