8.8 Required Reporting of Adverse Events

Physicians' professional commitment to advance scientific knowledge and make relevant information available to patients, colleagues, and the public carries with it the responsibility to report suspected adverse events resulting from the use of a drug or medical device.

Mandated pre- and post-marketing studies provide basic safeguards for public health, but are inherently limited in their ability to detect rare or unexpected consequences of use of a drug or medical device. Thus spontaneous reports of adverse events, especially rare or delayed effects or effects in vulnerable populations are irreplaceable as a source of information about the safety of drugs and devices. As the professionals who prescribe and monitor the use of drugs and medical devices, physicians are best positioned to observe and communicate about adverse events.

Cases in which there is clearly a causal relationship between use of a drug/device and an adverse event, especially a serious event, will be rare. Physicians need not be certain that there is such an event, or even that there is a reasonable likelihood of a causal relationship, to suspect that an adverse event has occurred. A physician who suspects that an adverse reaction to a drug or medical device has occurred has an ethical responsibility to:

(a) Communicate that information to the professional community through established reporting mechanisms.

(b) Promptly report serious adverse events requiring hospitalization, death, or medical or surgical intervention to the appropriate regulatory agency.

AMA Principles of Medical Ethics: I,V,VII

Background report(s):

CEJA 3-A-16 Modernized *Code of Medical Ethics*

CEJA Report B-A-93 Reporting adverse drug and medical device events

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CEJA Report B – A-93
Reporting Adverse Drug and Medical Device Events

BACKGROUND INFORMATION AND IMPORTANCE OF REPORTING

The Food and Drug Administration (FDA) operates programs to collect and analyze data on adverse reactions to drugs and medical devices. These programs' origins can be traced to the AMA's efforts in the mid-1950s to register cases of drug-induced blood dyscrasias, particularly aplastic anemia caused by chloramphenicol.[1,2] The FDA established its own reporting system a few years thereafter. By 1961, both the AMA's and the FDA's registration systems had expanded to include all adverse reactions to drugs.[2] The AMA Registry concentrated on reports from physicians and smaller hospitals, while the FDA focused on collecting information from larger hospitals, universities, and government.[2] In 1962, the Food and Drug Act was amended to require drug manufacturers to report adverse drug reactions to the FDA.[1] The dual reporting system continued until 1970, when the AMA dissolved its Registry because of underreporting and the existence of the FDA's program.[2]

The need continues unabated for a spontaneous physician reporting system for adverse events suspected to be caused by drugs or medical devices. Although new drugs and devices are not approved for marketing until numerous studies have been completed, premarketing studies cannot guarantee product safety. Such studies are limited by the small numbers of patients involved and by the populations being studied. Rarely are more than 3000 patients involved in preapproval clinical studies of drugs, and rarely do studies last more than three years.[1,3] Any uncommon side effects, delayed effects, or consequences of long-term drug administration would not be observed before the drug is marketed. Additionally, the patient population used in clinical trials does not usually include vulnerable populations such as the elderly, the young, women, those with complicated disease, or those taking other medications.[3] Information about interactions with these special populations, then, will likely not be revealed in premarketing studies but will only become available after the new product is on the market.

Formal postmarketing studies have become more common and sophisticated, but they too suffer from inherent deficiencies and are limited by the number of subjects. For example, in order to detect the difference between an adverse reaction incidence rate of 1/5000 and 1/10,000, some 306,000 patients would have to be observed,[4] far more than any study could achieve. Spontaneous reporting may thus be the only affordable method for detecting reactions that occur less frequently than 1 in 10,000.[5] Besides being the most efficient way of noting rare effects, spontaneous reporting may be the only practical way of observing long-term effects or some drug interactions. To take the drastic step of forbidding marketing of a drug until all long-term consequences and interactions are identified through formal research would impose unacceptable costs in the form of untreated or inadequately treated illness.

For these reasons, postmarketing surveillance outside of formal studies constitutes a vital activity in ensuring the safety of drugs and devices. The usefulness of spontaneous reporting of adverse drug reactions is well documented. Case examples of adverse reactions detected by physicians' reporting include pseudomembranous colitis associated with lincomycin,[6] flank pain syndrome associated with suprofen,[7] and most recently, serious reactions to temafloxacin that resulted in its voluntary recall.[8] Up to 50% of new chemical entities undergo a change in their labeling based primarily upon adverse event reporting.[9]

Spontaneous reporting systems do have limitations. They may be slow, influenced by romotional claims and the media, and unable to provide data from which incidence rates can be calculated.[10] Causality may be difficult to determine. Nevertheless, they remain the best, and perhaps only, method of gathering information about rare or delayed events, long term effects, drug interactions, and vulnerable populations. As one commentator has observed,

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> the imposition of formal Phase IV [postmarketing] schemes...must not lead physicians to underestimate their own importance in the discovery of new information about drugs. Spontaneous reporting by the alert and competent physician will, for the foreseeable future, remain the most important source of new leads about drugs.[4]

Despite the recognized importance of adverse event reporting, reporting rates in the United States are low compared with those in other developed countries.[11] For instance, physicians here report at approximately 25% of the rate in Denmark, and 50% of the rate in the United Kingdom.[10] The reasons offered for physicians' underreporting are many and varied. They include a lack of awareness of the FDA reporting system, complacency about drug safety, fear of legal liability, guilt about patient harm, and uncertainty regarding causation.[11] Recent FDA programs conducted with selected state health departments, however, have shown that physician reporting can be increased by a factor of four to seventeen with sustained professional education that includes frequent mailings, oral presentations at health care sites, and journal articles and advertisements.[3]

REVIEW OF LEGAL ASPECTS

Physicians' liability concerns in reporting are understandable. Reports to manufacturers are potentially discoverable in litigation in some states and in some cases have been discovered by plaintiffs' attomeys.[12] Reports to the FDA are substantially protected,[13-15] and the FDA is considering, at the request of the AMA, instituting regulations that would preempt state discovery laws and better protect the confidentiality of physician reporters and their patients when reports are made to manufacturers.

Although drug and device manufacturers are required by law to report their knowledge of adverse events to the FDA, physician reporting remains voluntary in most cases. The only exceptions are the special categories of adverse reactions to vaccines,[16] and adverse device reactions resulting in serious injury or death to a patient.[17] In addition, the Joint Commission on Accreditation of Healthcare Organizations requires the reporting of all adverse drug reactions in hospitals.[18] While direct physician reports of adverse events account for only a small percentage of reports received by the FDA, the degree of dependence upon physician reporting should not be underestimated: many of the manufacturers' reports also originate with practicing health care professionals.[19] Moreover, the FDA individually reviews every direct report from a physician, unlike those from manufacturers, because physicians' reports generally inform of more serious reactions and are more complete.[3] One third of the direct reports from care providers in 1985 concerned hospitalization or death.[19] After reviewing reports, the FDA takes appropriate action, such as seeking additional information, conducting studies, or taking regulatory action.[20] The value of physicians' reports is reflected in the observation that although they constitute only a fraction of received reports, they account for a much greater proportion of labeling changes.[3]

In short, physicians' observations of suspected adverse reactions and reports to a central program are essential for identification of many detrimental effects of therapeutic interventions. Spontaneous reporting continues to playa vital role in acquiring knowledge because studies cannot overcome many of their inherent limitations. Physicians are well situated to gather the necessary information because they prescribe and monitor the use of medical drugs and devices. If they fail to observe or report, it is unlikely that any other group can generate similar data.

ETHICAL CONSIDERATIONS

Principle V of the AMA's Principles of Medical Ethics states that:

> A physician shall continue to study, apply and advance scientific knowledge, [and] make relevant information available to patients, colleagues, and the public...21

To fulfill this principle, physicians report to others their suspicions or knowledge of adverse reactions to drugs or devices. The purpose of any requirement to disseminate knowledge is to benefit patients and advance their level of care. The benefits to patients of having physicians participate in an adverse event reporting system are substantial and obvious. Previously unknown complications can be identified and the incidence of known complications can be better calculated. Profiles of types of reactions for a group of drugs can be obtained.[1] Particularly vulnerable patient populations can be identified and better protected. Informed consent can be enhanced through the conveyance of more accurate information.

Conversely, failure to participate in a reporting system can result in dangers remaining unknown and harm occurring to patients. Given their unique position and the importance of spontaneous reporting systems, physicians have an obligation to participate.

The Council has recognized a similar duty in the context of communicating information about new medical procedures:

Physicians have an obligation to share their knowledge and skills and to report the results of clinical and laboratory research. This tradition enhances patient care, leads to the early evaluation of new technologies, and permits the rapid dissemination of improved techniques.[22]

Physicians who have access to information that can benefit patients, whether a new technique or research results, have an obligation to share that information with colleagues and others. A similar obligation pertains in the situation where a physician observes a potential adverse reaction: the physician should make the event known and disseminate that knowledge among the larger medical community. In some cases, the physician may want to submit a report or letter to a medical journal. In addition, the physician may want to inform the manufacturer, if known, of the suspect drug or device. In all cases involving serious adverse events, the physician should report the event to the FDA, the government organization charged with ensuring the safety of drugs and medical devices.

When more than one physician observes an adverse drug or device event in a patient, great care must be taken to ensure that the reporting process is not jeopardized by confusion over which physician should do the actual reporting. In general, the duty to report applies to any physician who observes an adverse event, regardless of whether the physician was involved in the prescription of the suspect drug or device for the patient. If several physicians observe the same specific event in a patient, the duty to report should fall first to the physician who actually prescribed the suspect drug or device. If the prescribing physician is not aware or does not believe that an adverse event has occurred, then anyone of the physician observers should report it. The reporting of the event is far more important than who reports it. If a physician is in doubt about whether an observed adverse event has been reported, either by the prescribing physician or another physician observer, then that physician should report the event himself or herself. Multiple reports of the same specific adverse event may be superfluous, but failure to report the event at all results in deprivation of valuable information that can benefit patient and public health.

This obligation to report asks very little of physicians. Identifying adverse drug or device reactions is already an integral aspect of medical practice because such reactions often enter differential diagnoses.

Basic medical practice requires that the possibility of adverse reactions be entertained both in prescribing and in diagnosing. The lone additional duty is that of communication, which is not a difficult one to fulfill. The current FDA reporting form for drugs is less than one page in length and requests only basic information concerning the patient and the observed reaction. It is mailed periodically to health care professionals in the FDA's *Medical Bulletin,* and is also available in the *Physicians Desk Reference* and the AMA's *Drug Evaluations.* Although additional paperwork of any sort should not lightly be imposed in this period of regulatory burdens, completion of the standard form is not time-consuming and can have a significant impact on future patient care. Reports of adverse reactions to medical devices or food products can be made to the appropriate FDA division, and the FDA has recently streamlined its reporting procedures so that a single form can be used to report all kinds of adverse events, including events believed to be caused by nonprescription drugs, biologicals, nutritional supplements, and other FDA-regulated products.[23] In addition, the FDA has instituted a toll-free telephone line for requesting the reporting form and has made provisions for reports made by computer modem or fax.[23] The inconvenience involved in reporting is not as burdensome as some may believe, add should not deter physicians from providing the FDA with valuable information.

The most important adverse events to report are those that are serious. The FDA defines a serious adverse drug event as one involving an outcome of death, a life-threatening condition, initial or prolonged hospitalization, disability, or congenital anomaly, or when intervention was required to prevent permanent impairment or damage.[19,23,24] This definition may change, however, and physicians should keep abreast of what reports the FDA seeks.

As a final note, physicians should not fail to report a suspected adverse event or reaction because they cannot prove a causal link. Ethical constraints may prohibit challenging the patient, and some information on causation may result from the accumulation of many individual reports. The FDA requests that all *suspicions* of serious events be reported,[25] a policy that accords with the goal of protecting the public health.

Opinion 9.081: Reporting Adverse Drug or Device Events

A physician who suspects the occurrence of an adverse reaction to a drug or medical device has an obligation to communicate that information to the broader medical community, including, in the case of a serious adverse event, the Food and Drug Administration (FDA). Spontaneous reports of adverse events are irreplaceable as a source of valuable information about drugs and medical devices, particularly their rare or delayed effects, as well as their safety in vulnerable patient populations. Although premarketing and mandated postmarketing studies provide basic safeguards for the public health, they suffer from inherent deficiencies that limit their ability to detect rare or unexpected consequences of drug or medical device use. Physicians who prescribe and monitor the use of drugs and medical devices constitute the group best able to observe and communicate information about resulting adverse events.

Serious adverse events are the most important to report and are the only adverse events for which the FDA desires a report. The FDA considers an adverse event to be serious when the patient out- come is death, a life-threatening condition, initial or prolonged hospitalization, disability, or congenital anomaly, or when intervention was required to prevent permanent impairment or damage. Certainty, or even reasonable likelihood, of a causal relationship between the drug or medical device and the serious adverse event will rarely exist and is not required before reporting the event to the FDA. Suspicion of such a relationship is sufficient to give rise to an obligation to participate in the reporting system.

[Opinion 9.081 is derived from Principles I, V, and VII of the Principles of Medical Ethics]

REFERENCES

1. Faich GA. Adverse-drug-reaction monitoring. *N Engl J Med.* 1986;314:1589-1592.

2. Lee B, Turner WM. Food and Drug Administration's adverse drug reaction monitoring program. *Am J Hosp Pharm.* 1978;35:929-932.

3. Scott HD, Thatcher-Renshaw A, Rosenbaum SE, Waters,Jr WJ, Green M, Andrews LG, Faich GA. Physician reporting of adverse drug reactions: Results of the Rhode Island adverse drug reaction reporting project. *JAMA.* 1990;263: 1785-1788.

4. Lasagna L. Discovering adverse drug reactions. JAMA. 1983;249:2224-2225.

5. Rossi AC, Knapp DE. Discovery of new adverse drug reactions.JAMA. 1984;252:1030-1033.

6. Venning GR. Identification of adverse reactions to new drugs. *Br Med J.* 1983;286: 199-202.

7. Rossi AC, Bosco L, Faich GA, Tanner A, Temple R. The importance of adverse reaction reporting by physicians: suprofen and the flank pain syndrome.]AMA. 1988;259: 1203-1204.

8. Severe adverse reactions prompt recall of new antibiotic. *Food Drug Cosmetic Law Reports* June 29, 1992) 1549:1-2.

9. US General Accounting Office. *FDA Drug Review: Post Approval Risks* 1976-1985. Washington, DC: General Accounting Office; 1990.

10. Edlavitch SA, Adverse drug event reporting: Improving the low US reporting rates. *Arch Int Med.* 1988;148:1499-1503.

11. Rogers AS, Israel E, Smith CR, Levine D, McBean AM, Valente C, Faich G. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Arch Int Med.* 1988;148:1596-1600.

12. Newsome v. Breon Laboratories, Inc., 709 S.W. 2d 559, 560 (Tenn. 1986).

13. FDA Medication and Device Problem Report; see also 21 C.F.R. § 314.81(h).

14. 21 C.F.R. § 314.81(1).

15. 21 U.S.C. § 360i(b)(3).

16. 42 U.S.C. §§ 300aa-14, 300aa-25.

17. Safe Medical Devices Act, Public L. No.101-629.

18. *Accreditation Manual* 1993. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations.

19. Faich GA, Knapp D, Dreis M, Turner W. National adverse drug reaction surveillance: *1985. JAMA.* 1987;257:2068-2070.

20. Turner WM, Milstien JB, Faich GA, et al. The processing of adverse reaction reports at FDA. *Drug*

lnfo J. 1986;20:147-150.

21. Principles of Medical Ethics: Principle V. *Current Opinions of the Council on Ethical and Judicial Affairs of the AMA.* Chicago, IL: American Medical Association; 1992.

22. Opinion 9.08: New Medical Procedures. *Current Opinions of the Council on Ethical and judicial Affairs of the AMA.* Chicago, IL: American Medical Association; 1992.

23. Kessler DA. Introducing MED Watch: A new approach to reporting medication and device adverse effects and product *problems. JAMA.* 1993; 269:2765-2768.

24. 21 C.F.R. § 803.3(h) (1991).

25. Kennedy DL, Johnson JM, Nightingale SL. Monitoring of adverse drug events in *hospitals. JAMA.* 1991;266:2878.