Introducing MEDWatch

A New Approach to Reporting Medication and Device Adverse Effects and Product Problems

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UNFORTUNATELY, many health professionals do not think to report adverse events that might be associated with medications or devices to the Food and Drug Administration (FDA) or to the manufacturer. That needs to change, and the FDA is taking steps to encourage that to happen.

Reports from health professionals of adverse events or product quality problems are essential to ensure the safety of drugs, biologicals, medical devices, and other products regulated by the FDA once they are introduced into the US market.

Even the large, well-designed clinical trials that are conducted to gain premarket approval cannot uncover every problem that can come to light once a product is widely used. A new drug application, for example, typically includes safety data on several hundred to several thousand patients. If an adverse event occurs in perhaps one in 5000 or even one in 1000 users, it could be missed in clinical trials but pose a serious safety problem when released to the market. Moreover, patients taking marketed drugs in conjunction with other drugs may experience interactions not revealed during the premarketing phase.[1]

In response to voluntary reports from physicians to the FDA or the manufacturer, the FDA has issued warnings, made labeling changes, required manufacturers to conduct postmarketing studies, and ordered product withdrawals that have ultimately prevented patient deaths and suffering.

Adverse drug reports from physicians, for example, prompted the FDA to determine that torsades-de-pointes ventricular arrhythmias could occur when the antihistamine terfenadine (Seldane) was taken in combination with the antifungal medicine ketoconazole or the antibiotic erythromycin.[2] This episode also increased recognition that individual variability in drug metabolism can account for significant differences in patient response[1] and underscored the importance of postmarketing studies and physician observations and reports.

Other examples of FDA actions prompted by reports of adverse events include the 1986 recall of suprofen,[3] the 1991 alert to health professionals on potentially fatal latex hypersensitivity,[4] the 1992 boxed warning and alert to physicians regarding use of angiotensin-converting enzyme inhibitors during the second and third trimesters of pregnancy,[5] and, most recently, the recall of temafloxacin.[6]

Just as reports enable us to respond to serious adverse events, lack of reporting can delay problem detection. Silicone breast implants are one example. Although these devices have been on the market for some 30 years, only recently has evidence accumulated about a possible association with autoimmune-like disorders.[7,8] If reports from physicians who diagnosed autoimmune-like disorders in patients with breast implants had been received years ago, the possible connection might have been identified much earlier.

Aside from adverse events associated with specified vaccines (listed in the National Childhood Vaccine Injury Act[9]), most reporting by health providers is voluntary. Manufacturers of drugs and devices and device distributors are required to report adverse events,[10,11] and soon manufacturers of biologicals will face similar requirements. Device manufacturers and distributors are also required to report to the FDA product problems that may cause death or serious injury if the malfunction were to recur.[11] Health care facilities are required to report certain adverse events associated with devices.[11] However, these groups, like the FDA, depend on health care professionals' surveillance and voluntary reporting.

Although the FDA receives many adverse event reports, these probably represent only a fraction of the serious adverse events encountered by providers. A recent review article[12] found that between 3% and 11% of hospital admissions could be attributed to adverse drug reactions. Only about 1% of serious events are reported to the FDA, according to one study.[13]

There are probably several reasons why some serious events are not reported to either the FDA or the manufacturer. First, when confronted with an unexpected outcome of treatment, physicians may not consider drug-induced or device-induced disease, but rather consider the event to be related to the course of the disease.

Unfortunately, this may be due to the limited training medical students receive in clinical pharmacology and therapeutics. A 1985 survey of US medical schools found that only 14% of them had required courses in core skills and principles of therapeutic decision making and clinical pharmacology. Of the remainder, 87% taught only a few hours of clinical pharmacology, and most of the teaching occurred in the early years of medical training.[14]

Another factor inhibiting physician reporting is that it is not an ingrained practice—it is not in the culture of US medicine to notify the FDA about adverse events or product problems. In other countries such as the United Kingdom, adverse drug reporting is more frequent.[15] A patchwork of reporting forms and systems may make it difficult to file reports in the United States and may discourage even the most conscientious professionals. Finally, physi-

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A complete list of the participants in the Working Group appears at the end of this article.

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. XXXXXXXXX See OMB statement on reverse

FDA Use Only

Triage unit sequence #

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — ☐ female ☐ male
4. Weight — ___ lbs or ___ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model # ___
   catalog # ___
   serial # ___
   lot # ___
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 for more information or to report quality problems
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

Left and above, portions of the new MEDWatch reporting form.

cians may be unclear as to what adverse reactions should be reported to the FDA.

Mindful of these problems, the FDA has just completed an overhaul of the adverse event reporting system. This month we are announcing our new system called MEDWatch: The FDA Medical Products Reporting Program. (Adverse events associated with vaccines will continue to be reported through the Vaccine Adverse Event Reporting System [VAERS], a joint program of the FDA and the Centers for Disease Control and Prevention.[9])

This new system encourages health care professionals to regard reporting as a fundamental professional and public health responsibility. It was developed with the enthusiastic support of the medical community, and its success will depend on close cooperation among the FDA, the medical community, and industry to identify and report adverse events and problems with medications and devices.

The FDA recognizes that the confidentiality of the identities of both providers who report adverse events and patients is an important concern of health professionals. To encourage reporting, the FDA carefully protects the identities of providers who report and patients contained in FDA records and will not release such information to the public. Unfortunately, during the course of litigation manufacturers have increasingly been asked to reveal the identities of those reporting adverse events and, in some cases, even the identities of patients. The FDA believes that maintaining the confidentiality of these individuals is extremely important, and it has participated in a number of court cases vigorously opposing release of the names of those involved in adverse event reports. To date, we have been successful in maintaining the confidentiality of this information in all the cases in which we have been involved. Nevertheless, we are considering whether additional actions may be appropriate to further strengthen our ability to safeguard the confidentiality of this information.

Our goal in introducing MEDWatch is to underscore the responsibility of providers to identify and report adverse events that may be related to FDA-regulated products. To that end, we want to (1) make it easier for providers to report serious events, (2) make it clear to physicians and others what types of reports the FDA wants to receive, (3) more widely disseminate information on the FDA's actions that have resulted from adverse event and product problem reporting, and (4) increase physician understanding and awareness of drug- and device-induced disease.

HOW TO REPORT

Under the MEDWatch program, the separate forms previously used to report adverse drug reactions, drug quality product problems, device quality product problems, and adverse reactions to medical devices have been consolidated into a single, one-page reporting form for health professionals. This form can also be used to report problems with other FDA-regulated products, such as dietary supplements, cosmetics, medical foods, and infant formulas.

In addition to making reporting easier for providers, using one form for both device and drug problems should also help the health care community to detect, and the FDA to investigate, adverse events.

One example of how this form might facilitate investigation was the FDA's discovery that the latex-cuffed barium enema tips used to perform many barium enema procedures provoked life-threatening allergic responses in some patients.[4] When the problem was first recognized, practitioners typically believed that patients were reacting to the barium sulfate or to other medications used in the procedure, and therefore adverse incidents were initially reported as barium sulfate reactions to the Center for Drugs. The new one-page form asks reporters to indicate concomitant devices as well as the suspect drug and other drugs used in the procedures. Using the new form might have decreased the follow-up time required by FDA officials, the time needed to identify latex as the problem, and the time until the medical community was alerted.

The unified reporting form (Figure) will be available in several publications, including the *Physicians' Desk Reference*, the *FDA Medical Bulletin*, and *AMA Drug Evaluations*. A 24-hour-a-day, 7-day-a-week toll-free number, (800) FDA-1088, is also now available for providers who want to request forms or obtain the new *FDA Desk Guide to Adverse Event and Product Problem Reporting*.

Providers will no longer be expected to send different reports for devices and medications to different addresses at the FDA; there will now be a single mailing address for these reports. In addition, health professionals will be able to report electronically by computer by calling (800) FDA-7737 and responding to the questions that appear on the screen. Reports can be also sent to the FDA by fax ([800] FDA-0178) or by regular mail using the self-mailer included in the form.

In addition to reporting adverse events to the FDA, reports can also be sent to manufacturers, which are required by law to forward reports to the FDA.[10,11] If the event has occurred in a health care facility, reports of problems with medical devices should also be filed with that facility, which legally must

report device problems to the FDA and/or the manufacturer.[11]

The Joint Commission on Accreditation of Healthcare Organizations also has standards for monitoring and reporting adverse medication and device events.[16] Individual institutions may have their own procedures and guidelines for monitoring and reporting adverse events within the institution; physicians can obtain that information from the pharmacy and therapeutics committee or the institutional risk manager at their institution.

WHAT TO REPORT

Physicians should report when there is a *suspicion* that the drug or device may be related to a serious adverse effect; they are not expected to establish the connection or even to wait until evidence seems compelling. Reports should be alert of possible associations. Combined with other reports, follow-up, and results of epidemiologic studies or new studies undertaken, the FDA can evaluate these initial suspicions.

On the other hand, the FDA does not want providers to report every adverse reaction observed; this would not be practical for the practitioner or useful to the FDA. The FDA's goal is to increase reporting of *serious* events, not all adverse events. What should be reported are those cases in which the physician suspects that an FDA-regulated product was associated with a serious outcome—death, a life-threatening condition, initial or prolonged hospitalization, disability, or congenital anomaly, or when intervention was required to prevent permanent impairment or damage.

Although traditionally problems with devices are associated with products that are defective or malfunction, adverse events can occur with a device even when no malfunction or defect is recognized, for example, hypersensitivity to latex[4] or dialyzer germicides.[17]

Especially important to report are adverse effects from medications or devices that have been on the market for a relatively short time—about 3 years or less—because that is when the most critical problems are discovered. Since most serious adverse events are observed in the hospital setting,[18] practitioners should be especially diligent about reporting these events.

The FDA should also be informed promptly of product quality problems such as defective devices, inaccurate or unreadable product labeling, packaging or product mix-up, contamination or stability problems, and particulate matter in injectable products. In 1990, a total of 38 drug recalls resulted from reporting of such problems.[19] While pharmacists or risk managers are often the ones in a position to observe these problems, physicians who become aware of such problems should bring them to the FDA's attention by calling (800) FDA-1088 and submitting a report.

One recent example of the importance of this type of report is the possible link reported between hyperkalemia observed in two patients in a medical center intensive care unit and two enteral feeding products. The university's laboratory analysis demonstrated that the products had a potassium content about twice that specified on the label. The FDA follow-up of this report revealed that all product lines of the manufacturer contained potassium values of 150% to 250% of the declared amount. Because these products are frequently used as a sole source of nutrition, and sometimes in patients with compromised renal function, the FDA initiated a recall of the product.

PROVIDE PHYSICIAN INFORMATION

MEDWatch is aimed at facilitating reporting by providers, but we also want to better inform providers about regulatory actions taken by the FDA in response to reports. We believe this information will not only be useful to physicians and others, but that it will also encourage serious adverse event reporting by demonstrating the value of the information. The FDA will therefore take a more aggressive stance in reporting back to providers.

ENHANCE PHYSICIAN UNDERSTANDING

As part of MEDWatch, the FDA hopes to heighten physician awareness of drug- and device-induced disease. Our educational efforts will include a focus on issues such as the importance of the problem, mechanisms of adverse drug and device reactions, and how to evaluate possible adverse events. As part of that effort we plan to hold a conference for health care professionals and FDA officials to help poise practitioners to recognize drug- and device-induced problems when they occur, and thereby increase participation in the MEDWatch program.

MEDWatch is an important program that we hope will significantly improve our ability to monitor the safety of products we regulate and to take necessary actions swiftly and effectively. Perhaps most important, we hope MEDWatch will encourage an increased sense of responsibility among physicians and other health care providers about reporting adverse events and product problems. We are eager to work closely with the medical community to ensure the program's success.

Leaders of the Working Group include the following: Sharon Natanblut, MPA; Dianne Kennedy, MPH, RPh; Eliot Lazar, MD; Peter Rheinstein, MD, JD, MS. Members of the Working Group include Chuck Anello, ScD; Dave Barash, RPh; Ilisa Bernstein, PharmD; Ross Bolger, RPh; Kay Cook, JD; Mary Pat Couig, RN, MPH; Jerry Donlon, MD, PhD; Joyce Johnson, DO, MA; Catherine Lorraine, JD; Tom McGinnis, RPh; John Nazario, RPh; Stuart Nightingale, MD; Carl Peck, MD; Mary Pendergast, JD; Suresh Rastogi, PhD; Chet Reynolds, MBA; Renie Schapiro, MPH; Linda Tollefson, DVM; Ann Wion, JD.

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