



## THE CLINICAL IMPACT OF ADVERSE EVENT REPORTING

### Learning Objectives:

Upon completion of this program, health professionals should be able to:

- Identify underlying principles of postmarketing surveillance
- Understand reporting requirements (health professionals, manufacturers, user facilities) regarding regulated medical product safety
- Discuss basic limitations/strengths of data derived from postmarketing surveillance
- List examples of FDA regulatory actions that have been based on postmarketing surveillance
- Describe how FDA disseminates information regarding medical product safety
- Understand how a national postmarketing surveillance program impacts clinical practice

### Stephen A. Goldman, MD

Assoc. Dir. for Medicine, MEDWATCH  
Office of the Commissioner, FDA

### Faculty:

#### Dianne L. Kennedy, RPh, MPH

Director, MEDWATCH  
Office of the Commissioner, FDA

#### David J. Graham, MD, MPH

Acting Chief, Epidemiology Branch  
Center for Drug Evaluation and  
Research, FDA

#### Thomas P. Gross, MD, MPH

Director, Division of Postmarket  
Surveillance, Center for Devices and  
Radiological Health, FDA

#### Richard M. Kapit, MD

Chief, Adverse Events Section  
Center for Biologics Evaluation and  
Research, FDA

#### Lori A. Love, MD, PhD

Director, Clinical Research and  
Review Staff, Center for Food Safety  
and Applied Nutrition, FDA

#### Gale G. White, MS, RN

Deputy Director, MEDWATCH  
Office of the Commissioner, FDA

**N**omifensine (Merital<sup>®</sup>), an antidepressant that had been available in Germany since 1976, had been prescribed to an estimated ten million patients prior to its marketing in the U.S. in July, 1985<sup>1,2</sup>. Initial labeling for the product reflected a variety of long-recognized hypersensitivity reactions, including fever, liver injury, hemolytic anemia and eosinophilia, that were apparently all readily reversible<sup>3</sup>.

At the time of U.S. approval, FDA was aware of reports of less than twenty hemolytic anemia cases, all non-fatal; however, in 1985, when foreign adverse reaction reports showed the hemolytic anemia might be fatal, labeling was revised to reflect the potential seriousness of the reaction<sup>3</sup>. Due to an increase in serious hemolytic anemia cases seen in Europe, marketing of nomifensine was reconsidered by the manufacturer, who announced a worldwide withdrawal of the drug on January 21, 1986<sup>3,4</sup>.

The case of nomifensine illustrates that the safety profile of a drug evolves over its lifetime on the market. Even after almost ten years experience, or longer, new information that will impact the clinical use of a medical product can be detected. Consequently, all medical products need to be continually assessed for safety within the context of their perceived benefit.

Medical product safety monitoring is an ongoing process accomplished through **Postmarketing Surveillance**, the collection of data about drugs [or any other medical product] once they are marketed and thus available to the general population<sup>5</sup>. This process encompasses adverse event reports evaluation, generation of safety-related hypotheses and use of techniques to evaluate these hypotheses.

### THE NEED FOR POST-MARKETING SURVEILLANCE

While the U.S. has one of the most rigorous approval processes in the world, it is not possible to detect all potential problems during premarketing clinical trials. Medical product studies, ranging

from preclinical animal testing and medical device bench testing to final tests in humans, have inherent limitations no matter how well they are designed or conducted. The need for postmarketing surveillance is a direct result of these limitations.

### Premarketing Animal Studies

Most medical products are first tested in animals prior to introduction into humans. Animal studies have limitations in their ability to predict human toxicity; this is demonstrated by the case of practolol, a  $\beta_1$ -adrenoreceptor blocking agent withdrawn from the U.K. market in 1976 after several years of widespread use<sup>6,7</sup>, and never marketed in the U.S.

The U.K. action was prompted by the serious adverse reactions of dermatitis, keratoconjunctivitis and sclerosing peritonitis, collectively termed the oculomucocutaneous syndrome<sup>6,7</sup>. This syndrome had not been seen during extensive preclinical animal testing conducted within required guidelines<sup>7</sup>.

Subsequent toxicity studies in several small animal species (both those that metabolize practolol similarly to humans and those whose practolol metabolism is more extensive than humans) found no animal model for the observed human adverse reactions<sup>8</sup>. The lack of reproduction of these particular adverse reactions in any laboratory animal species<sup>9</sup> demonstrates that animal studies, no matter how appropriate or well-performed, are not necessarily predictive of human pathology.

### Premarketing Human Clinical Studies

There are intrinsic limitations to premarketing human clinical trials with respect to their ability to detect adverse events. Short duration, narrow population, narrow set of indications and small size are major factors in this regard<sup>10</sup>, irrespective of the type of medical product being studied.

The capability of premarketing clinical trials to discover rare adverse events is

particularly affected by their size. In order to have a 95% chance of detecting an adverse event with an incidence of 1 per 1,000, 3,000 patients at risk are required<sup>11</sup>; with no more than 3,000 to 4,000 individuals usually exposed to a medical product prior to marketing, only those adverse events with approximately 1/1,000 or greater incidence can be expected to be found.

While medical products are usually studied for several years before they are marketed, an individual patient in a clinical trial is generally exposed to the product for less than a year. Even long-duration premarketing clinical trials, which can last several years, do not provide the degree of patient exposure that will occur postmarketing with a chronically used medical product. In addition, the relatively short durations of clinical trials mitigate against the detection of adverse events with long latency.

Because of these limitations, premarketing clinical trials seldom detect or define the frequency of all important adverse events. As a result, the official labeling/product information at the time of approval of a medical product reflects what is known about that product's risk at that point in time. The controlled environment under which clinical trials are conducted means that the safety data presented in the original labeling of a product usually represents actual occurrence rates in the defined population that has been studied.

### Postmarketing Experience

Health professionals should be aware that this is **not** the case with postmarketing data. Once a product leaves the controlled study environment and enters general clinical use, the ability to detect the actual incidence of an adverse event can essentially be lost. On the other hand, once a new product is marketed, there are great increases in the number and variety of patients exposed, including those with multiple medical problems and undergoing treatment with numerous concomitant medical products.

As a result, the population experience with the product will be much broader than that derived from the clinical trials. One particular safety-related advantage this offers is a generally greater capability

to detect adverse events possibly related to interactions with other medical products than is available in the premarketing phase.

**The major changes in the size and nature of the exposed patient population that occur once a medical product is available for widespread use emphasize the great importance of adverse event detection and reporting by health professionals.**

### MEDWATCH

It is with these considerations in mind that MEDWATCH, the FDA Medical Products Reporting Program, was established<sup>12</sup>. While FDA's longstanding postmarketing surveillance programs predate MEDWATCH, this educational/promotional initiative was designed to emphasize the responsibility of healthcare providers to identify and report adverse events related to the use of medical products. Through the MEDWATCH program health professionals can report serious adverse events and product problems that occur with such medical products as drugs, biologics, medical and radiation-emitting devices, and special nutritional products (e.g., medical foods, dietary supplements and infant formulas).

**Causality is not** a prerequisite for MEDWATCH reporting; **suspicion** that a medical product may be related to a serious event is sufficient reason for a health professional to submit a MEDWATCH report. However, a report on every adverse event is **not** sought - what is desired is an increase in the reporting of **serious** events. In that regard, TABLE 1 offers a guideline for adverse event reporting. However, health professionals are welcome to report any adverse event that they judge to be clinically significant.

**TABLE 1** MEDWATCH  
What is a Serious Event?

- Any event that is
- Fatal
  - Life-threatening
  - Permanently/significantly disabling
  - Requires or prolongs hospitalization
  - Congenital anomaly
  - Requires intervention to prevent *permanent* impairment or damage

### CLINICAL SYNOPSIS 1

#### BIOLOGICS

#### Intravenous Immunoglobulin and Aseptic Meningitis Syndrome

In early 1994, FDA learned of a report from the National Institutes of Health (NIH), which described a high rate of aseptic meningitis syndrome (AMS) occurring in patients being treated for neuromuscular diseases with high doses of intravenous immunoglobulin (IGIV). The patients had been receiving doses of 2 g/kg of IGIV, which is five to ten times higher than the normally recommended dosage. Six of 54 patients developed severe headache, meningismus, and fever within 24 hours of dosing. Cerebrospinal fluid (CSF) was consistent with AMS in four of the six.

Following this lead, 22 cases of IGIV-associated AMS which had been reported to the FDA were reviewed. Symptoms included fever and photophobia, and prominent painful headache. Twenty of the cases were associated with positive CSF findings, including leukocytosis (predominantly neutrophilic) and elevated protein.

Unexpectedly, 19 of the reports indicated that normal doses of IGIV had been administered (0.2 - 0.4 g/kg). The patients had been treated by withdrawal of the medication and administration of analgesics. Of particular note was the characteristic time course of IGIV-associated AMS. The illnesses all began between 12 and 24 hours after administration, and recovery ensued within several days following withdrawal of the medication.

As a result of this work, FDA and NIH workers published two articles on IGIV-AMS simultaneously in the same journal<sup>45,46</sup>. The FDA also directed IGIV manufacturers to modify labeling to include a Precaution statement about the occurrence of the syndrome.

### POSTMARKETING REPORTING OF ADVERSE EVENTS

The FDA has the regulatory responsibility for ensuring the safety of all marketed medical products. Health professionals are critical to this process, in that the first hint of a potential problem originates with

the perceptive clinician who then reports the case to the appropriate source. It is important for all health professionals to be aware that some reporting is mandated by federal law and regulation while other reporting, although considered vital, is strictly voluntary.

### By Health Professionals

Any postmarketing surveillance program depends on health professionals to report serious adverse events observed in the course of their everyday clinical work. Except for adverse events associated with specified vaccines, reporting by an individual health professional is voluntary.

Given the clinical importance of postmarketing surveillance, all healthcare providers (physicians, pharmacists, nurses, dentists and others) should look upon adverse event reporting as part of their professional responsibility. The American Medical Association<sup>13</sup> and American Dental Association<sup>14</sup> advocate (respectively) physician and dentist participation in adverse event reporting systems as an obligation<sup>13,14</sup>. Further, *The Journal of the American Medical Association* instructs its authors that adverse drug or device reactions should be reported to the appropriate government agency, in addition to submitting such information for publication<sup>15</sup>.

Health professionals can use the voluntary MEDWATCH form to report adverse events or product problems related to any medical product, with the exception of those occurring with vaccines. Reports can be sent to FDA either directly or, in most cases, via the manufacturer.

Reports concerning vaccines should be sent to the Vaccine Adverse Event Reporting System (VAERS), a joint program of the FDA and the Centers for Disease Control and Prevention<sup>16</sup>. Certain events following immunization (e.g., paralytic poliomyelitis after oral poliovirus vaccine)<sup>17</sup> are mandated by the National Childhood Vaccine Injury Act of 1986 to be reported, but VAERS accepts all reports of suspected significant adverse events after any vaccine administration<sup>16</sup>. For more information on VAERS, call 1-800-822-7967.

Health professionals working in a hospital or other **user facility** (nursing home, ambulatory surgical facility, outpa-

tient treatment facility and outpatient diagnostic facility) should be aware of the legal requirements for medical device-related reporting by user facilities mandated by the Safe Medical Devices Act of 1990 (SMDA) (see TABLE 2<sup>18</sup>). Under the SMDA, physicians' offices are excluded from the user facility definition and thus exempt from mandatory reporting requirements. The FDA likewise excludes

TABLE 2

#### Medical Device Reporting (MDR) Requirements<sup>18</sup>

**NB:** days refers to working days, unless otherwise specified

- **User Facility:**
  - **Deaths** (to FDA and manufacturer within 10 days)
  - **Serious injuries/illnesses** (to manufacturer within 10 days; to FDA if manufacturer unknown, also within 10 days)
  - **Semiannual Reports** (to FDA) of all reports sent to FDA and/or manufacturer (due January 1 and July 1)
- **Manufacturer:**
  - **Deaths, serious injuries, malfunctions** (to FDA within 30 calendar days of becoming aware of event)
  - **"5-day Report"** [to FDA if become aware of 1) event(s) necessitating "remedial action to prevent an unreasonable risk of substantial harm to the public health" or 2) reportable event for which FDA has requested 5-day report]
  - **Annual Certification** of number of reports
- **Distributor:**
  - **Deaths** (to FDA and manufacturer within 10 days)
  - **Serious injuries/illnesses** (to FDA and manufacturer within 10 days)
  - **Malfunctions** (to FDA and manufacturer within 10 days)

other groups that perform similar functions to physicians' offices (e.g., dentists, optometrists, nurse practitioners) from mandatory reporting<sup>18</sup>. However, health professionals within a user facility should familiarize themselves with their institu-

tion's procedures for device-related reporting, and actively participate in the program.

**Confidentiality:** The FDA acknowledges that health professionals have concerns regarding their confidentiality as reporters, and that of the patients whose cases they report. In order to encourage reporting of adverse events, FDA regulations offer substantial protection against disclosure of the identities of both reporters and patients. This was further strengthened on July 3, 1995, when a regulation went into effect extending this protection against disclosure by preempting state discovery laws regarding voluntary reports held by pharmaceutical, biological and medical device manufacturers<sup>19</sup>.

### By Hospitals

The FDA, recognizing the valuable role that hospitals play in the detection of adverse events and problems with medical products, views every active hospital monitoring program as a vital component of the national postmarketing surveillance system. Hospital reporting of adverse events, both within and outside an individual facility, is a mixture of voluntary and mandatory reporting.

Adverse event monitoring by hospitals is linked to Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards. In order to be accredited, JCAHO requires each hospital to monitor for adverse events involving pharmaceuticals and devices, with medication monitoring to be a continual collaborative function<sup>20</sup>. JCAHO standards indicate that medical product adverse event reporting should be done per applicable law/regulation, including those of state/federal regulatory bodies<sup>20</sup>.

The American Society of Health-System Pharmacists (ASHP) has also been instrumental in the evolution of active internal hospital adverse drug event (ADE)-monitoring systems. ASHP guidelines include delineated criteria for classifying an adverse drug reaction (ADR) as significant<sup>21</sup>, unlike JCAHO standards, which do not mandate a specific definition for a serious ADE. ASHP guidelines specifically state serious or unexpected ADRs should be reported to FDA, manufacturer, or both<sup>21</sup>.

As user facilities, hospitals are sub-

ject to mandatory federal medical device adverse event reporting. TABLE 2 (on previous page) outlines these requirements, which include reporting by the facility of suspected medical device-related deaths to both FDA and the manufacturer, and serious injuries/illnesses to the manufacturer or to FDA, if the manufacturer is unknown<sup>18</sup>. However, there are no federal laws or regulations that require hospitals to report pharmaceutical-related adverse events to the FDA, although they are strongly encouraged to do so regarding those events deemed serious.

#### Reporting Required By Law or Regulation

Reporting by individual healthcare providers is essentially voluntary. However, manufacturers and distributors of FDA approved pharmaceuticals (drugs and biologics) and medical devices plus pharmaceutical packers and device user facilities, all have mandatory reporting

**TABLE 3**  
Adverse Event (AE) Reporting Requirements for Pharmaceuticals<sup>22,23</sup>

- **15-day "Alert Reports":** each AE both serious and unexpected (i.e, not in the product's current labeling) must be reported to the FDA within 15 working days
- **Periodic AE Reports:** all non-15 day AE reports must be reported periodically (quarterly for the first three years after approval, then annually)
- **Other:** the frequency of reports of 1) AEs that are both serious and expected, and 2) therapeutic failures must be periodically monitored, and any significant increase must be reported within 15 days
- **Scientific Literature:** a 15-day report based on scientific literature (case reports, results from a formal clinical trial; epidemiology-based studies or "analyses of experience in a monitored series of patients")
- **Postmarketing Studies:** no requirement for a 15-day report on an AE acquired from a postmarketing study unless manufacturer concludes pharmaceutical causation for AE "reasonable possibility"

requirements.

TABLE 3 outlines mandatory reporting regarding pharmaceuticals<sup>22,23</sup>. By regulation, these companies are required to report **all** adverse events of which they are aware to the FDA and to provide as complete information as possible. As can be seen, mandated pharmaceutical reporting relies heavily on information provided by health professionals through both voluntary reporting and the scientific literature.

In the case of over-the-counter (OTC) drugs, reports are only required on OTC products marketed under an approved New Drug Application (NDA), including those prescription drugs that undergo a switch to OTC status. Reports are **not** required for other OTC drugs (i.e., older drug ingredients which are marketed without an NDA), although voluntary reporting is encouraged.

Both prescription and OTC drugs require FDA safety and efficacy review

#### CLINICAL SYNOPSIS 2

##### MEDICAL DEVICES

#### Barium Enema Kits and Sudden Death

Three reports of sudden death associated with the use of barium enema kits were reported to the FDA. The first case, reported in 1989, involved a 49 year-old female with a history of atopic dermatitis, allergic rhinitis and asthma who was undergoing a barium enema for occult blood in her stool when she reported the onset of an allergic reaction<sup>47</sup>. The study was immediately terminated, but within minutes she began to have increasing dyspnea, then became cyanotic. The patient was intubated, and underwent unsuccessful resuscitation efforts<sup>47</sup>.

In April 1990, two more cases of sudden death associated with the use of barium enema kits were reported. A 41 year-old female complained of nausea shortly after insertion and inflation of the tip/cuff assembly, went into cardiac arrest within 30 seconds and underwent unsuccessful resuscitation efforts. In the third case, a 72 year-old female had an immediate reaction after the tip portion of the tip/cuff assembly was inserted prior to introduction of the barium contrast agent, went into vascular collapse and died.

Review of the adverse event database revealed no other reports of reactions to barium enema procedures. However, literature review showed a potential problem with reactions to devices containing latex<sup>48</sup>, of which the barium enema cuffs are made. Various FDA investigations were undertaken, including collection of samples of gloves, devices and lubricants.

As a result, the manufacturer of the enema tips voluntarily agreed to send out an urgent Medical Alert to approximately 10,000 radiologists that notified them of adverse reactions possibly associated with latex allergy that could occur during barium enema procedures. Minimizing use of tips with retention

cuffs was requested, as was the use of non-cuffed tips whenever possible. Physicians were urged to screen patients for latex allergy histories and concomitant drug use.

Further regulatory actions were subsequently taken:

1) Health Hazard Evaluation of the tips/cuffs lead to the recommendation that the Medical Alert be expanded to include more health professionals and organizations. The firm added an additional washing of the cuffs in the manufacturing process and wrote a letter to all health professionals concerning allergic reactions associated with the use of barium enema products with latex cuffs;

2) After a second Health Hazard Evaluation determined that the problems associated with these devices presented a high risk of serious adverse health consequences, the firm initiated a recall of all latex cuffed enema tips;

3) An ad hoc FDA committee that was formed to consider additional action developed an FDA Medical Alert which outlined the occurrence of several severe allergic reactions to medical devices containing latex and suggested ways to screen and protect allergic patients. This was sent to approximately 1,000 radiological and medical organizations, and was published in the July 1991 *FDA Medical Bulletin*;

4) Manufacturers of latex devices received an FDA letter discussing how to manufacture latex products in order to minimize the possibility that latex contaminants are either a source of, or contributing factor to, adverse reactions to various types of latex devices.

These events led to a 1992 International Conference on latex sensitivity and the practice of physicians testing patients for latex sensitivity prior to undergoing surgical procedures.

prior to marketing, unlike dietary supplements (which include vitamins, minerals, amino acids, botanicals and other substances used to increase total dietary intake). By law<sup>24</sup> the manufacturers of dietary supplements do not have to prove safety or efficacy, so the onus is on the FDA to prove that a particular product is unsafe. As a result, direct-to-FDA voluntary health professional reporting of serious adverse events possibly associated with dietary supplements is particularly important.

TABLE 2 (on page 3) lists the medical device-related reporting required of user facilities, manufacturers, and distributors<sup>18</sup>.

All unsolicited reports from health professionals received by FDA via either the voluntary or mandatory route are called **spontaneous** reports. A spontaneous report is a clinical observation that originates outside of a formal study<sup>25</sup>. The combination of adverse event information generated by **all** reporting makes up the database upon which postmarketing surveillance depends.

## LIMITATIONS & STRENGTHS OF SPONTANEOUS REPORTS DATA

As with clinical trials, there are important limitations to consider when using spontaneously reported adverse event information. These limitations include difficulties with adverse event recognition, underreporting, biases, estimation of population exposure and report quality.

### LIMITATIONS

#### Adverse Event Recognition

The recognition of ADEs [or any other medical product-associated adverse event] is quite subjective and imprecise<sup>26</sup>. While an attribution between the medical product and the observed event is assumed with all spontaneously reported events, every effort is made to rule out other explanations for the event in question. It is well known that placebos<sup>27</sup> and even no treatment<sup>28</sup> can be associated with adverse events. In addition, there is almost always an underlying background rate for any clinical event in a population, regardless of whether there was exposure to a medical product.

Reaching a firm conclusion about the relationship between exposure to a medical product and the occurrence of an adverse event can be difficult. In one study, clinical pharmacologists and treating physicians showed complete agreement less than half the time when determining whether medication, alcohol or "recreational" drug use had caused hospitalization<sup>29</sup>.

Such considerations emphasize the crucial need for careful, thoughtful review of adverse event reports upon their receipt by FDA or the manufacturer. It is through this process that causality, or at least a high degree of suspicion for a product-adverse event association, is put to the test.

#### Underreporting

Another major concern with any spontaneous reporting system is underreporting of adverse events<sup>16,30-32</sup>. It has been estimated that rarely more than 10% of serious ADRs, and 2-4% of non-serious reactions, are reported to the British spontaneous reporting program<sup>30</sup>. A similar estimate is that the FDA receives by direct report less than 1% of suspected serious ADRs<sup>32</sup>. This means that cases spontaneously reported to any surveillance program, which comprise the **numerator**, generally represent only a small portion of the number that have actually occurred. The effect of underreporting can be somewhat lessened if submitted reports, irrespective of number, are of high quality.

#### Biases

Unlike clinical trial data, which are obtained under strictly controlled conditions, spontaneously reported information is uncontrolled, and therefore subject to the possible influence of a number of biases that can affect reporting. These biases include the length of time a product has been on the market, country, reporting environment, detailing time and quality of the data<sup>33</sup>. A striking illustration of the impact one such factor can have is the finding that the peak of spontaneous ADR reporting for a drug is at the end of the second year of marketing, with a subsequent precipitous decline in reporting<sup>34</sup> despite a lack of apparent decline in usage or change in ADR incidence<sup>34,33</sup>. In addition to these biases, it is possible that reported cases might differ from nonre-

ported cases in characteristics such as time to onset or severity<sup>35</sup>

#### Estimation of Population Exposure

Compounding these numerator limitations is the lack of **denominator** data, such as user population and drug exposure patterns<sup>35</sup>, that would provide the exact number of patients exposed to the medical product, and thus at risk for the adverse event of interest. Numerator and denominator limitations make incidence rates computed from spontaneously reported data problematic<sup>35</sup>, if not completely baseless. However, even if the exposed patient population is not precisely known, estimation of the exposure can be attempted through the use of drug utilization data<sup>36</sup>.

This approach, whose basic methodologies are applicable to medical products in general, can be of great utility. Major sources of data on the use of drugs by a defined population include market surveys based on sales or prescription data, third-party payers or health maintenance organizations, institutional/ambulatory settings or specific pharmacoepidemiological studies<sup>36</sup>. Cooperative agreements and contracts with outside researchers enable FDA to utilize such databases in its investigations. Device utilization studies employ the same sources of data, as well as Medicare-derived information.

Care must be taken in interpreting results from studies utilizing these databases. That drug prescribing does not necessarily equal drug usage<sup>36</sup>, and the applicability of results derived from a specific population (such as Medicaid recipients) to the population at large, need to be weighed carefully.

#### Report Quality

The ability to assess, analyze and act on safety issues based on spontaneous reporting is dependent on the quality of information submitted by health professionals in their reports. A complete adverse event report should include the following: product name (and information such as model and serial numbers in the case of medical devices); demographic data; succinct clinical description of adverse event, including confirmatory/relevant test/laboratory results; confounding factors (such as concomitant medical products and medical history); temporal

information, including date of event onset and start/stop dates for use of medical product; dose/frequency of use (as applicable); biopsy/autopsy results (as applicable); dechallenge/rechallenge information (if available); and outcome.

Given the limitations of spontaneously reported data, what are its strengths?

### STRENGTHS

#### Large-Scale and Cost-Effective

Two vital advantages of surveillance systems based on spontaneous reports are that they potentially maintain ongoing surveillance of all patients, and are relatively inexpensive<sup>37</sup>. In fact, they are probably the most cost-effective way to detect rare, serious adverse events not discovered during clinical trials.

#### Generation of Hypotheses and Signals

Making the best possible use of the data obtained through monitoring underlies postmarketing surveillance<sup>38</sup>. Towards that goal, the great utility of spontaneous reports lies in **hypothesis generation**<sup>31</sup>, with need to explore possible explanations for the adverse event in question. By fostering suspicions<sup>39</sup>, spontaneous report-based surveillance programs perform an important function, which is to generate **signals** of potential problems that warrant further investigation.

Assessment of the medical product-adverse event relationship for a particular report or series of reports can be quite difficult. TABLE 4 lists factors that are helpful in evaluating the strength of association between a drug and a reported adverse event<sup>40</sup>.

TABLE 4

#### Useful Factors For Assessing Causal Relationship Between Drug and Reported Adverse Event<sup>40</sup>

- Chronology of administration of agent, including beginning and ending of treatment and adverse event onset
- Course of adverse event when suspected agent stopped [dechallenge] or continued
- Etiologic roles of agents and diseases in regard to adverse event
- Response to readministration [rechallenge] of agent
- Laboratory test results
- Previously known toxicity of agent

### CLINICAL SYNOPSIS 3

#### SPECIAL NUTRITIONALS

#### L-tryptophan Related Eosinophilia-Myalgia Syndrome<sup>49</sup>

In July 1989, a healthy 44 year-old woman in Santa Fe with a history of allergic rhinitis started taking L-tryptophan, an essential amino acid available as a dietary supplement, for insomnia. By early September she was reporting onset of cough, shortness of breath and weakness. When first seen by a physician in late September, she presented with a puffy, flushed face, abdominal pain, mucosal ulcers, myalgia and weakness. Her white blood cell (WBC) count was 11,900 cells/mm<sup>3</sup>, with an eosinophil count of 42%. Her condition worsened through October, with her WBC rising to 18,200 and eosinophil count to 45%.

Her physician consulted with a rheumatologist, who while not knowing what was wrong with this patient, did know of a second patient who had been hospitalized in Santa Fe with similar symptoms and eosinophil count. In mid-October, a third patient in New Mexico, who had an eosinophil count of 9,000 and had also been taking L-tryptophan, was discovered. While one patient was unusual and two was suspicious, three made it a cluster of a very uncommon disease.

All three original patients were middle-aged women. Although the severity differed, all had the common features of myalgia, weakness, oral ulcers, abdominal pain, shortness of breath and skin rash. While the doses of L-tryptophan they had used were similar, the duration of use prior to onset of illness varied from a few weeks to 2 years. Common laboratory features included striking leukocytosis, eosinophilia, elevated aldolase [with a normal creatine kinase (CK)] and abnormal liver function tests.

An article about the condition appeared in the November 7 *Albuquerque Journal News*. On November 11, FDA issued a Public Advisory against the use of L-tryptophan, followed four days later by the Centers for Disease Control and Prevention (CDC) establishment of a system of national state-based surveillance for the newly named eosinophilia-myalgia syndrome (EMS)<sup>49</sup>.

On November 17, FDA requested a nationwide recall of all over-the-counter dietary supplements in capsule or tablet form providing 100 mg or more of L-tryptophan in a daily dose. On March 23, 1990, because of the identification of one case of EMS associated with a dietary supplement containing less than 100 mg, and continued efforts by some firms to circumvent the recall, the agency requested an expansion of the recall to all marketed products containing added manufactured L-tryptophan. Excepted were those that were permitted to contain added L-tryptophan under existing food additive regulations. Additionally, on March 22, the agency had imposed an import alert to detain all foreign shipments of manufactured L-tryptophan.

Because virtually all manufactured L-tryptophan is imported into the U.S., the practical effect of the recall and import alert was to effectively eliminate the availability of L-tryptophan-containing dietary supplements. Eventually, more than 1,500 cases of EMS, including 38 deaths, have been reported to the CDC, although the true incidence of the disorder is thought to be much higher.

The recognition of a cluster of cases was the key to the detecting of EMS. Interactions among various specialists, including a family physician, hematologist, rheumatologist, clinical immunologist and epidemiologists, was crucial to this process<sup>49</sup>.

Of equal importance is ongoing basic and clinical research to explain the etiology and pathogenesis of this disorder. Although it is widely believed that contaminants or impurities in the L-tryptophan are responsible for EMS, continuing research indicates a role for "pure" tryptophan itself<sup>50-52</sup>, as well as for certain host factors in the etiology of the disorder<sup>53,54</sup>. These findings support suggestions that the L-tryptophan-associated EMS was caused by several factors and is not necessarily related to a contaminant in a single source of L-tryptophan.

FDA concerns about the safety of L-tryptophan-containing products and the possibility of potential new cases of L-tryptophan-related EMS are underscored by recent information indicating the availability of L-tryptophan by American sources. Both EMS's clinical seriousness, and uncertainties surrounding its etiology, indicate the need for health professionals to remain vigilant regarding adverse events possibly associated with the use of L-tryptophan-containing dietary supplements, and to report such events to MEDWATCH.

The stronger the drug-event relationship in each case and the lower the incidence of the adverse event occurring spontaneously, the fewer case reports are needed to perceive causality<sup>41</sup>. It has been found that for rare events, coincidental drug-event associations are so unlikely that they merit little concern, with greater than three reports constituting a signal requiring further study<sup>35</sup>. In fact, it has been suggested that a temporal relationship between medical product and adverse event, coupled with positive dechallenge and rechallenge, can make isolated reports conclusive as to a product-event association<sup>42</sup>. Biological plausibility and reasonable strength of association aid in deeming any association as causal<sup>30</sup>.

However, achieving certain proof of causality through postmarketing surveillance is unusual<sup>41</sup>. Attaining a prominent degree of suspicion is much more likely, and may be considered a sufficient basis for regulatory decisions<sup>41</sup>.

#### Clinician Contribution

The reliance of postmarketing surveillance systems on health professional reporting enables an individual to help improve public health. This is demonstrated by one study that found direct practitioner participation in the FDA spontaneous reporting system was the most effective source of new ADR reports that led to changes in labeling<sup>43</sup>. Ensuring that the information provided in the adverse event report is as complete and in depth as possible further enhances postmarketing surveillance.

**Thus, while possessing inherent limitations, postmarketing surveillance based on spontaneous reports data is a powerful tool for detecting adverse event signals of direct clinical impact. It is dependent not only on health professional participation, but also on the quality of the reports that are submitted.**

#### FDA EVALUATION OF REPORTS OF ADVERSE EVENTS

The very uncontrolled nature of spontaneously reported data places great importance on the evaluation of submitted reports of adverse events. This process is perhaps most accurately characterized as a method, applied on a case-by-case basis, that is based on experience, knowledge of the medical product being monitored and awareness of the limitations of the data.

All reports from health professionals (direct reports) and specific reports from manufacturers are individually reviewed by an FDA health professional safety evaluator, with particular attention to all reported serious adverse events that are not in labeling in the case of pharmaceuticals<sup>44</sup>. All other reports are entered into the database for use in aggregate analysis. In focused evaluation of adverse events, the postmarketing surveillance database is searched for other reports, and further steps such as literature searches and use of medical product utilization databases may be taken.

Based on careful review of spontaneous reports, the FDA can initiate various actions, including a "Dear Health Professional" letter or Safety Alert; labeling, name or packaging change(s); conducting further epidemiologic investigations; requesting manufacturer-sponsored postmarketing studies; conducting inspections of manufacturers' facilities/records; or working with a manufacturer regarding possible withdrawal of a medical product from the market.

Four clinical synopses<sup>44-55</sup> provided by each of the four participating FDA Centers that outline examples of regulatory actions based on postmarketing surveillance are presented throughout the article. The clinical synopses demonstrate the step-wise process of spontaneous reports evaluation that is utilized at the FDA. In addition, these cases clearly illustrate that a single adverse event report from a health professional can often lead to an FDA action that has clinical importance.

At times signals generated by the spontaneous reporting system are of sufficient strength that further epidemiologic investigation is not necessary, a situation exemplified by the clinical synopses. However, non-epidemiologic types of studies may be indicated, such as those attempting to explain the etiology of eosinophilia-myalgia syndrome<sup>50,53,54</sup>.

Should formal epidemiologic study be deemed useful in regard to an adverse event, well-validated methods can be utilized by FDA, industry, and academia in their investigations\*. For example, FDA regulation of oral contraceptives has relied heavily on the findings of case-control and cohort studies<sup>56</sup>.

\*A future MEDWATCH Continuing Education Article will focus on the use of epidemiologic principles and methods in the study of medical product safety.

# Adverse reaction?

## If it's serious, we need to know.

1-800-FDA-1088.

**FDA MEDWATCH**  
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

If it's serious, we need to know.

#### DISSEMINATION OF SAFETY-RELATED INFORMATION

Keeping medical product labeling/package inserts up to date is an ongoing, dynamic process that depends on new information gleaned from spontaneous adverse event reports. Remaining current with changes in medical product information can be an imposing task for the busy health professional. As a result, an important public health aspect of postmarketing surveillance is the dissemination of safety-related information to the clinical community.

The FDA, in concert with the product's manufacturer, informs health professionals of the most serious and pressing safety issues through such mechanisms as "Dear Health Professional" letters, Safety Alerts, Public Health Advisories, Talk Papers and Urgent Notices. Two recent examples demonstrating this educational process are outlined in TABLE 5.

TABLE 5

#### Examples of Safety-Related FDA Notifications

##### • Retinal Photoc Injuries From Operating Microscopes During Cataract Surgery:

Despite all efforts taken to minimize the risks of retinal damage, retinal photic injuries from the light sources used in operating microscopes during cataract surgery and other intraocular procedures may occur. Several factors appear to be important determinants of photic retinal injury. These include: angle of light incidence, light intensity, exposure time, and intensity of the blue light component. FDA recommends several actions to reduce the risk of retinal photic injury and reminds physicians about the reporting requirements of the Safe Medical Devices Act of 1990. [October 16, 1995 FDA Public Health Advisory]

##### • FDA Requires Labeling Change on Lindane-Containing Lice Treatments:

Lindane is generally safe and effective when used according to the approved directions, but its overuse can be harmful. FDA has recommended labeling changes that encourage lindane's use only for patients who have either failed to respond to adequate doses of, or are intolerant of, other approved therapies. In addition, product labeling will advise health care providers and parents not to confuse prolonged itching with reinfestation. The label already warns parents that neurotoxicity is possible for certain patients, especially infants. [April 3, 1996 FDA Talk Paper]

The population of health professionals to whom individual notifications are distributed is not always universal, and is dependent on the medical product and the provider specialties most likely to be involved. As a result, other methods are used to reach the broadest possible health professional audience. The MEDWATCH column in the *FDA Medical Bulletin*, which is distributed to 1.2 million health professionals nationwide, seeks to enhance general awareness by summariz-

ing the most recent notifications.

In addition, MEDWATCH utilizes its Partner program to disseminate new safety-related information. To date, over 100 health professional organizations have joined FDA as Partners and work with MEDWATCH to increase awareness of, and participation in, postmarketing surveillance. Notifications like Safety Alerts are provided to the Partners as they are released, with the information in turn distributed by the Partners to their members.

It is important for health professionals to be aware that not all changes in medical product information necessitate use of mechanisms such as a "Dear Health Professional" letter. These are reserved for only the most serious and pressing adverse events. While the *Physicians' Desk Reference*<sup>®</sup> contains official labeling for most drugs and can be reviewed periodically for changes, FDA is currently looking at other ways, including the Internet, by which new safety-related information can be made more readily available to health professionals.

#### SUMMARY

The effectiveness of a national post-marketing surveillance program is directly dependent on the active participation of health professionals. The limitations of premarketing clinical trials in detecting adverse events make the safety profile of any medical product an evolving, ongoing process contingent on the availability of up-to-date information derived from postmarketing clinical experience.

Despite the limitations of spontaneous reports, FDA's program for the surveillance of regulated medical product safety provides vital information of clinical importance. The identification of problems, and the subsequent dissemination of safety-related information to the clinical community at large, begins with reports from astute health professionals.

By viewing adverse event reporting as a professional responsibility, and recognizing that the quality of data generated from spontaneous reports is determined by the quality of the submitted information, health professionals can play a major role in improving the public health.

#### CLINICAL SYNOPSIS 4

#### DRUGS

#### Temafloxacin and Hemolytic Anemia

Temafloxacin, a fluoroquinolone antibiotic, was first marketed in January, 1992. By early April, FDA had received a few reports of hemolytic anemia occurring in patients treated with this drug. Over the next two months, many additional cases were reported, eventually totaling nearly 100. These provided a clear picture of what was subsequently called the "temafloxacin syndrome"<sup>55</sup>.

The typical patient was a young woman with no underlying medical conditions who was treated for urinary tract infection with temafloxacin. Within 7-10 days of starting treatment, dark colored urine was often noted, sometimes with accompanying flank pain and chills. There was typically a drop in hemoglobin of 3 grams or greater. Acute renal failure developed in nearly two thirds, with hemodialysis usually required. Mild hepatobiliary changes were noted in half the patients, and coagulopathy in one third.

A subset of patients experienced the syndrome after their first dose of temafloxacin. That these patients were more likely to have had prior exposure to a fluoroquinolone antibiotic provided support for an antibody-mediated basis for massive hemolysis.

On the basis of spontaneously reported cases, the manufacturer, in consultation with FDA, voluntarily withdrew temafloxacin from the market worldwide in June, barely six months after initial marketing.

In 1994, FDA staff published a multicase review article describing the "temafloxacin syndrome"<sup>55</sup>.

#### Acknowledgements

The MEDWATCH program would like to thank Mary W. Brady, RN, MSN, Suzanne E. Rich, RN and Marie H. Reid, RN, BSN (CDRH) for their contributions to the medical device clinical synopsis. In addition, the editorial contributions of Vincent F. Guinee, MD, MPH and Robert C. Nelson, PhD (CDER) are gratefully acknowledged.

## REFERENCES

1. Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm* 1986;5:471-480
2. Kinney JL. Nomifensine maleate: a new second-generation antidepressant. *Clin Pharm* 1985;4:625-636
3. Nomifensine withdrawn by manufacturer. *FDA Drug Bull* 1986;16:7-8
4. Hoechst-Roussel Pharmaceuticals Inc. Withdrawal of Merital. Somerville, NJ: Hoechst-Roussel Pharmaceuticals Inc, January 1986
5. Mamelok RD. Drug discovery and development. In: Melmon KL, Morrelli HF, Hoffman BB, Nierenberg DW, eds. *Melmon and Morrelli's Clinical Pharmacology: Basic Principles in Therapeutics*. 3rd ed. New York: McGraw-Hill, Inc; 1992:911-921
6. Venning GR. Identification of adverse reactions to new drugs. II--how were 18 important adverse reactions discovered and with what delays? *Br Med J* 1983;286:289-292
7. Wallender M-A. The way towards adverse event monitoring in clinical trials. *Drug Saf* 1993;8:251-262
8. Reeves PR, McCormick DJ, Jepson HT. Practolol metabolism in various small animal species. *Xenobiotica* 1979;9:453-458
9. Rosenbaum SE, Lindup WE, Orton TC. Practolol and its metabolites: tissue localization and retention in the hamster. *J Pharmacol Exp Ther* 1985;234:485-490
10. MEDWATCH Continuing Education Article. Clinical therapeutics and the recognition of drug-induced disease. Goldman SA, Kennedy DL, Lieberman R, eds. Rockville, Md: Food and Drug Administration, June 1995
11. Lewis JA. Post-marketing surveillance: how many patients? *Trends Pharmacol Sci* 1981;2:93-94
12. Kessler DA. Introducing MEDWATCH: a new approach to reporting medication and device adverse effects and product problems. *JAMA* 1993;269:2765-2768
13. American Medical Association. Reporting adverse drug and medical device events: report of the AMA's Council on Ethical and Judicial Affairs. *Food and Drug Law Journal* 1994;49:359-366
14. Advisory Opinion No. 1 to Section 4-A, Devices and Therapeutic Methods, of the American Dental Association Principles of Ethics and Code of Professional Conduct
15. The Journal of the American Medical Association. JAMA instructions for authors. *JAMA* 1996;275:5-12
16. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12:542-550
17. The National Childhood Vaccine Injury Act of 1986, at Section 2125 of the Public Health Service Act as codified at 42 U.S.C. 300aa-25(Suppl 1987)
18. 21 CFR 803 and 807
19. Protecting the identities of reporters of adverse events and patients; preemption of disclosure rules. *Fed Regist* 1995; 60(April 3);16962-16968
20. Joint Commission on Accreditation of Healthcare Organizations. 1996 Comprehensive Accreditation Manual for Hospitals. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations, 1995
21. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health Syst Pharm* 1995;52:417-419
22. 21 CFR 314.80
23. 21 CFR 600.80
24. Dietary Supplement Health and Education Act (DSHEA) of 1994
25. Faich GA. Adverse-drug-reaction monitoring. *N Engl J Med* 1986;314:1589-1592
26. Koch-Weser J, Sellers EM, Zacest R. The ambiguity of adverse drug reactions. *Eur J Clin Pharmacol* 1977;11:75-78
27. Green DM. Pre-existing conditions, placebo reactions, and "side effects". *Ann Intern Med* 1964;60:255-265
28. Reidenberg MM, Lowenthal DT. Adverse nondrug reactions. *N Engl J Med* 1968;279:678-679
29. Karch FE, Smith CL, Kerzner B, Mazzullo JM, Weintraub M, Lasagna L. Adverse drug reactions - a matter of opinion. *Clin Pharmacol Ther* 1976;19:489-492
30. Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? The William Withering Lecture 1994. *J R Coll Physicians Lond* 1995;29:41-49
31. Strom BL, Tugwell P. Pharmacoevidence: current status, prospects, and problems. *Ann Intern Med* 1990;113:179-181
32. Scott HD, Rosenbaum SE, Waters WJ, Colt AM, Andrews LG, Juergens JP, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. *R I Med J* 1987;70:311-316
33. Sachs RM, Bortnichak EA. An evaluation of spontaneous adverse drug reaction monitoring systems. *Am J Med* 1986;81(suppl 5B):49-55
34. Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP, eds. *Advances in Inflammation Research*. Vol 6. New York: Raven Press; 1984:1-7
35. Begaud B, Moride Y, Tubert-Bitter P, Chaslerie A, Haramburu F. False-positives in spontaneous reporting: should we worry about them? *Br J Clin Pharmacol* 1994;38:401-404
36. Serradell J, Bjornson DC, Hartzema AG. Drug utilization study methodologies: national and international perspectives. *Drug Intell Clin Pharm* 1987;21:994-1001
37. Fletcher AP. Spontaneous adverse drug reaction reporting vs event monitoring: a comparison. *J R Soc Med* 1991;84:341-344
38. Finney DJ. The detection of adverse reactions to therapeutic drugs. *Stat Med* 1982;1:153-161
39. Finney DJ. Statistical aspects of monitoring for dangers in drug therapy. *Methods Inf Med* 1971;10:1-8
40. Standardization of definitions and criteria of causality assessment of adverse drug reactions: drug-induced liver disorders: report of an international consensus meeting. *Int J Clin Pharmacol Ther Toxicol* 1990;28:317-322
41. Auriche M, Loupi E. Does proof of causality ever exist in pharmacovigilance? *Drug Saf* 1993;9:230-235
42. Temple RJ, Jones JK, Crout JR. Adverse effects of newly marketed drugs. *N Engl J Med* 1979;300:1046-1047
43. Rossi AC, Knapp DE. Discovery of new adverse drug reactions: a review of the Food and Drug Administration's Spontaneous Reporting System. *JAMA* 1984;252:1030-1033
44. Turner WM, Milstien JB, Faich GA, Armstrong GD. The processing of adverse event reports at FDA. *Drug Information Journal* 1986;20:147-150
45. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994;121:259-262
46. Scribner CL, Kapit RM, Phillips ET, Rickles NM. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med* 1994;121:305-306
47. Feczko PJ, Simms SM, Bakirci N. Fatal hypersensitivity reaction during a barium enema. *AJR Am J Roentgenol* 1989;153:275-276
48. Ownby DR, Tomlanovich M, Sammons N, McCullough J. Anaphylaxis associated with latex allergy during barium enema examinations. *AJR Am J Roentgenol* 1991;156:903-908
49. Hertzman, PA. L-tryptophan related eosinophilia-myalgia syndrome. In: *Drug and Device Induced Disease: Developing a Blueprint for the Future*. Proceedings of a MEDWATCH Conference; 1994 Jan 21-22; Rockville, Md. Rockville, Md: FDA, 1994
50. Love LA, Rader JJ, Crofford LJ, Raybourne RB, Principato MA, Page SW, et al. Pathological and immunological effects of ingesting L-tryptophan and 1,1'-ethylidenebis (L-tryptophan) in Lewis rats. *J Clin Invest* 1993;91:804-811
51. Farnelli S, Mariani A, Grimaldi A, Mariani M, Iannesi A, De Rosa F. [Eosinophilia-myalgia syndrome associated with 5-OH-tryptophan. Description of a case]. *Recent Prog Med* 1991;82:381-384
52. Lampert A, Joly P, Thomine E, Ortolini JC, Lauret P. [Scleroderma-like syndrome with bullous morphea during treatment with 5-hydroxytryptophan, carbidopa and flunitrazepam]. *Ann Dermatol Venerol* 1992;119:209-211
53. Flockhart DA, Clauw DJ, Sale EB, Hewett J, Woosley RL. Pharmacogenetic characteristics of the eosinophilia-myalgia syndrome. *Clin Pharmacol Ther* 1994;56:398-405
54. Okada S, Sullivan EA, Kamb ML, Philen RM, Miller FW, Love LA. Human leukocyte antigen (HLA) DRB1 alleles define risk factors for the development of eosinophilia myalgia syndrome (EMS) [abstract]. *Arthritis Rheum* 1994;37(Suppl):S274
55. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: review of 95 cases. *Clin Infect Dis* 1994;18:946-950
56. Sobel S. The role of epidemiology in the regulation of oral contraceptives. *Public Health Rep* 1984;99:350-354