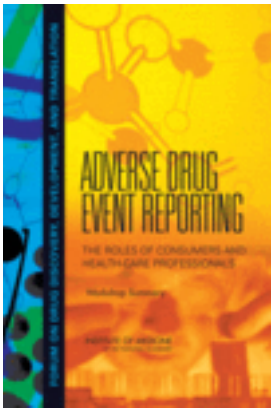

Adverse Drug Event Reporting: The Roles of Consumers and Health-Care Professionals: Workshop Summary

Forum on Drug Discovery, Development, and Translation, Jeffrey M. Drazen, Jennifer Rainey, Heather Begg, and Adrienne Stith Butler, Rapporteurs

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ADVERSE DRUG EVENT REPORTING

THE ROLES OF CONSUMERS AND HEALTH-CARE PROFESSIONALS

WORKSHOP SUMMARY

Jeffrey M. Drazen, Jennifer Rainey, Heather Begg,
and Adrienne Stith Butler, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Shawn C. Becker, Patient Safety Initiatives, U.S. Pharmacopeia Center for the Advancement of Patient Safety
Marc L. Berger, Outcomes Research & Management, Merck & Co., Inc.
Scott E. Campbell, Research Programs, American Diabetes Association
Edward Holmes, School of Medicine, University of California, San Diego

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Mel Worth,** Scholar-in-Residence, Institute of Medicine. Appointed by the National Research Council and Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Summary*

Adverse reactions to prescription drugs (adverse drug events, or ADEs) are quite common and usually do little harm to patients. But in a small percentage of cases, they can have serious consequences and can cause serious injury or death. All drugs must undergo extensive studies to examine their safety and efficacy before they receive FDA approval. As a result, the risk of adverse drug events is often well known in advance. However, these studies are conducted on a limited number of subjects, making it difficult to identify adverse reactions that are rare but potentially serious. Furthermore, because these studies are limited in duration, they may not identify reactions that occur over long periods of time.

In order to identify adverse drug events after a drug has been released, the Food and Drug Administration (FDA) relies on a postmarketing surveillance program known as MedWatch. Information collected through MedWatch is placed in a large database known as the Adverse Event Reporting System (AERS). There are significant concerns about the effectiveness of this system. Furthermore, the FDA has limited options for conducting follow-up safety assessment once a drug has been approved. As a result, serious adverse drug reactions may be fully appreciated only after a drug has been on the market for many years.

*The Forum's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

In November 2005, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation convened a workshop to explore issues associated with the reporting of ADEs. The workshop addressed the following questions: How can ADEs be effectively identified, particularly when the adverse effects are rare? How can the direct, causal effects of drugs be distinguished from simple associations? How can health-care professionals and their patients aid in the identification of drug-related adverse events? How can knowledge of ADEs be more effectively used in clinical practice?

IDENTIFYING ADVERSE DRUG EVENTS

Since the FDA has limited options for addressing safety questions about drugs after premarketing research has occurred, identifying ADEs requires the participation of health-care providers, consumers, and others. MedWatch, the FDA's program for postmarket surveillance, collects clinical information involving drugs from health-care professionals and consumers through a variety of channels, including mail, Internet, and telephone. The largest source of postmarket information on ADEs is drug companies themselves. Companies typically submit large numbers of reports at a time in batch form to the FDA. Data on adverse events are placed in the AERS, and are evaluated by FDA staff to detect safety signals and monitor drug safety.

Potential adverse events are also identified through case reports in the medical literature and through epidemiologic surveillance of electronic claims and other data. Surveillance systems screen claims data for adverse events and notify health-care providers who then determine if follow-up reporting is required. The Centers for Medicare and Medicaid Services captures data on drug use and clinical services for individual subscribers. And institutional review boards of individual health systems capture many adverse events in clinical trials.

Challenges associated with current systems for reporting ADEs were discussed by workshop participants. Underreporting and incomplete reporting and poor quality of data are concerns about all reporting systems. There have been suggestions that streamlining these systems and ensuring anonymity may motivate health-care providers to file adverse event reports with greater frequency and accuracy. Participants discussed the need for incentives to encourage the development of long-term safety studies. Furthermore, it was suggested that informing consumers about known drug risks and benefits may encourage consumer reporting of ADEs and participation in follow-up studies.

ESTABLISHING CAUSE AND EFFECT

Once a possible association between a drug and an adverse event is detected and reported, it is important to confirm whether the ADE is actually caused by the drug rather than due to the influence of some other confounding variable. In order to answer this question, studies must obtain adequate information about confounding factors, such as comorbidities, patient risk factors, and concurrent treatments. Furthermore, studies must be of sufficient duration to detect problems over time. Unfortunately, many postmarketing studies lack these basic characteristics. Participants suggested that researchers and clinicians discuss safety and efficacy in the early stages of protocol development in order to improve the subsequent postmarketing study design.

DRUG-DRUG INTERACTIONS

When attempting to understand cause and effect in ADEs, it is important to tease out single drug effects from effects due to the interaction of two or more drugs (drug-drug interactions, or DDIs). DDIs can make a medication less effective, cause unexpected side effects, or increase the action of a particular drug. There are multiple systems in place for capturing DDIs. However, these systems often disagree about which interactions have the greatest clinical importance. Participants discussed the need to establish uniform criteria for interactions and ADEs, and a standardized terminology to evaluate interactions for their clinical importance.

Several strategies for reducing DDIs were discussed, including a more active role for pharmacists and pharmacy benefit managers (PBM). PBMs electronically share information about drugs with health-care providers, manufacturers, and heath plan sponsors. These linked databases could potentially provide valuable information about reducing harm from inefficacy, drug interactions, and adverse drug reactions. Patient education is also an important step in the reduction of DDIs. The formation of a cross-disciplinary DDI working group that would create improved tools for communicating interactions and consequences was discussed. This group could identify and prioritize DDIs, develop a public database capable of receiving all new labeling information on drug interactions, perform an ongoing review of data from the FDA and the published literature, and possibly recommend specific interaction studies.

LABELING

Information on known ADEs and DDIs is not effectively communicated to clinicians and pharmacists. The drug label is the principal means of communication, and there are concerns about the presentation

and usefulness of the information it contains. One concern identified by participants is that all reported adverse reactions are included on labels, making it difficult for providers to assess the relative importance of different reactions. The FDA has recently changed the format of drug labels in an attempt to present the information more effectively. New drug labels have a highlights section in which manufacturers are required to place information obtained during the preceding year in order to keep physicians updated on new indications and interactions.

Another concern is that drug labels do not currently communicate the likelihood that a particular adverse event will occur when taking the drug. Participants suggested that labeling should inform consumers and physicians about the level of causal certainty of suspected adverse reactions. To make risk communication effective, the medical and scientific community, users, media, industry, and regulators must have a common understanding of the decision-making principles behind risk labeling, must agree on the meaning of terms such as *adverse reaction*, *adverse event*, and *risk,* and must use such terminology consistently.

Drug labels also do not communicate effectively a drug's potential side effects or interactions with other substances. Participants discussed the need for a third party (neither the FDA nor the pharmaceutical industry) to decide what information about DDIs is relevant to consumers and useful to prescribers and should therefore be included on labeling.

Several related FDA initiatives to improve drug safety were discussed. The electronic labeling rule requires industry to submit e-labels to the FDA beginning in June 2006. This rule requires bar-coding on all over-the-counter medications. Paperless labeling will eliminate the requirement for paper package inserts, which cost companies about $1 million per year per product. In order to address the rising demand for better drug safety surveillance, the American Board of Medical Specialties (ABMS) is developing a "Patient Safety" Module that will address drug safety in physician certification and recertification.

INCREASING CONSUMER INVOLVEMENT IN ADVERSE EVENT REPORTING

Because they are directly affected by ADEs, consumers have an incentive to report them to their clinicians or pharmacists. However, there are few efforts to more actively engage consumers in the process, and there is no comprehensive system in place for consumer reporting of adverse events. The fact that reporting systems such as MedWatch capture only a fraction of ADEs may be due, in part, to a lack of meaningful consumer engagement in this process.

Mechanisms that were discussed by workshop participants to increase

the involvement of consumers in ADE reporting included the development of outreach programs to provide the public with information about drugs and potential adverse effects. For example, the Consumers Union initiated the Best Buy Drugs website (www.crbestbuydrugs.org) to educate consumers about medications, specifically the drugs that give the best value. Increased ADE reporting can be encouraged through public service announcements, by direct-to-consumer advertising, and by providing consumers with multiple avenues for reporting events. Other suggestions discussed by participants included the formation of a drug safety oversight board with its own regulatory power, composed of consumer representatives and scientists with no industry ties or involvement in the approval process.

Increased involvement in reporting ADEs may also be achieved by looking to successful reporting programs, such as the United Kingdom's yellow card system. This system was presented as a potential model for a more integrated approach to voluntary reporting in the United States. The yellow card system is used to collect information from health professionals and consumers on suspected ADEs. It allows consumers to report online, by prepaid mail, and by phone. The system actively seeks reports and can be accessed in some form in almost any relevant care delivery setting, such as pharmacies and physician offices.

1

Introduction

Recent concerns about the unexpected adverse effects of marketed drugs, such as COX-2 (cyclooxygenase-2) inhibitors or specific statins, raise concerns not only about reporting these events during premarket studies, but also about the responsibility for ongoing surveillance of drugs once they are on the market (Psaty and Furberg, 2005). Sometimes serious adverse drug reactions are fully appreciated only after a drug has been on the market for years (Lasser et al., 2002). Therefore, when a drug is approved and released to the market, large numbers of patients will be exposed before all the potential adverse effects have been identified and thoroughly studied. Currently, there is no clearly defined process for addressing safety questions about drugs after premarketing research has occurred (Ray and Stein, 2006).

The problem of adverse drug events (ADEs) is a significant and troubling issue. In a study of Medicare consumers, the incidence of ADEs was determined to be 50.1 per 1,000 person-years of treatment (Gurwitz et al., 2003). The classes of drugs most frequently associated with ADEs were cardiovascular agents, antibiotics, diuretics, nonopioid analgesics, and anticoagulants. Of the reported ADEs, 38.0 percent were categorized as serious, life-threatening, or fatal.

Pre- and postmarket assessments of drugs are important for helping to identify ADEs. Premarket review addresses issues of efficacy and safety of a particular drug, and postmarketing surveillance examines rare adverse reactions, effects that can be appreciated only with long-term use, and off-label uses of FDA-approved drugs.

As Forum member Jeffrey Drazen noted, "Adverse events associated with treatments represent a major hurdle that is very difficult to overcome in the setting of the randomized clinical trials that are done when a drug gets approved for marketing. There is almost no other way . . . to see how the drug functions in the real world."

There are significant concerns about the process by which drugs are subject to assessment of their safety. While all drugs must undergo premarket studies examining effectiveness and safety before they receive FDA approval, these tests are conducted on a limited number of subjects and often do not investigate long-term outcomes (Ray and Griffin, 1993). In addition, drugs are not always used in practice the same way they were used in the studies that led to their approval. For example, patients taking the medication may differ from the population in which it was studied; the treated population may not be as closely monitored as the patients in the clinical trials; or drugs may be prescribed for off-label use, the common practice in which physicians prescribe a medication for a use other than that for which it was tested and approved. In addition, during the initial period after the introduction of a new drug, the likelihood of inappropriate dosing, failure to follow directions, and contraindicated use is high (Smalley et al., 2000; Graham et al., 2001; Griffin et al., 2004).

A rare adverse event, one that occurs in fewer than 1 in 1,000 treated patients (for example, aplastic anemia), may not be identifiable in the premarket data and generally becomes apparent only after the drug is in wide use after its approval by the FDA (Okie, 2005). Other adverse events are first recognized through case reports in the literature, for example, the association of cisapride and torsades de pointes (Ray, 2003). Additionally, if the drug increases the rate of a common condition—for example, if it increases the risk for an adverse vascular event such as heart attack or stroke—this may be identifiable only when many thousands or even millions of people have used the drug.

Postmarketing surveillance can address some of these concerns by studying use by a larger group of patients over a longer period of time than in the premarket phase. Postmarketing research also provides the opportunity for a more comprehensive evaluation of drug utilization in the clinical practice environment.

A limitation in postmarket observational studies is the potential for findings to be due to systematic differences between patients in the treatment and comparison groups, rather than to the drug that is the subject of the study. There are statistical techniques that can be employed to control for confounding factors, but they are only effective when the relationships are known in advance and the data are available (Hunter, 2006). Controlling for confounding factors is also difficult in studies involving causes of mortality. The contribution of medication effects to the overall

death rates may be small because drugs may exhibit a complex combination of effects—some protective and some adverse (Ray, 2005). Another challenge is variation in the actual utilization of medications by patients that may not be captured in administrative data, including poor patient compliance, the use of drug samples given to patients, and interactions with over-the-counter medications and dietary supplements.

The FDA's program for collecting postmarketing data is known as MedWatch. Information collected through MedWatch is placed in a large database known as the Adverse Event Reporting System (AERS). MedWatch collects ADE information from health-care professionals and consumers through a variety of channels, including mail, Internet, and telephone. The largest source of postmarket information on ADEs is drug companies themselves, which typically submit large numbers of ADE reports in batch form to the FDA.

AERS contains roughly 2.5 million health-care professional or lay-person-derived adverse event reports (Trontell, 2004).[1] The FDA searches these reports for serious or life-threatening outcomes that result in death, lead to hospitalization or disability, or require interventions to prevent clinically significant impairment. A larger investigation may be triggered by these reports. The primary purpose of reports sent to AERS is to serve as a platform for hypothesis generation rather than hypothesis testing (Strom, 2004).

Because there are few scientific standards for data collection, the information in the database can be incomplete, and the results derived can be difficult to interpret (Greenhill et al., 2003; Psaty et al., 2004). Detection of signals is limited to the low percentage of actual events that are reported to the database (less than 10 percent), the quality of the reports, and uncertain estimates of exposure (Brewer and Colditz, 1999). Rare events or outcomes not selected as end points for clinical development may not be appreciated until their occurrence in a wider patient population triggers suspicion among health-care professionals. In the United States, clinicians are not required to report suspected drug- or device-related adverse events. Even with the partial reporting that occurs, more than 400,000 ADE reports are submitted to the FDA each year. This, combined with the large number of products on the market, places a large burden on the roughly 100 members of the FDA's Office of Drug Safety to perform needed analyses of drug safety (Bennett et al., 2005).

In addition to AERS, the FDA requires drug companies to commit to conducting postmarketing studies for new drugs under the Accelerated Approval Program, the Animal Efficacy Rule, and the Pediatric Research

[1]As of publication, the AERS database contains more than 3.5 million reports (personal communication with Toni Piazza-Hepp, FDA, March 5, 2007).

Equity Act. The Accelerated Approval Program allows premarketing studies to use surrogate end points to predict clinical benefit, provided that postmarketing studies confirm the benefit. The Animal Efficacy Rule requires postmarket studies when animal data replace human data for ethical reasons. The Pediatric Research Equity Act enables the FDA to require pediatric studies of drugs already approved for adults before the drugs are labeled for children. However, 60 percent of postmarket studies that are tracked by the FDA are "pending," meaning that they have not commenced but have also not missed any deadlines (Phase IV Status Report, 2005).

The design and conduct of efficient and accurate postmarket drug surveillance studies must be considered a "cooperative venture between regulator, industry, and prescriber" (Wood, 1999). Some have called for the creation of a completely independent drug safety office (Psaty et al., 2004). The FDA has recently created an independent Drug Safety Oversight Board and a Drug Watch website to inform the public of adverse drug reactions (FDA, 2005a). Postmarketing surveillance data will still be submitted voluntarily, but the office will coordinate data with other government agencies such as the Centers for Medicare and Medicaid Services (CMS) and the Veterans Administration (VA). In addition to the formation of a new board, some also propose changes to the FDA's existing approval methods, such as "raising its threshold" for the approval of new drugs when effective alternatives already exist (Lasser et al., 2002) or for drugs designed to treat conditions where treatment is more of a convenience than a need (for example, a runny nose or male pattern baldness). However, increasing requirements for drug approval will delay new treatments from reaching the market.

The Medicare Part D benefit, in which millions of elderly Americans will receive reimbursement for prescription drugs, represents an enormous opportunity for engaging in postmarket studies. Through this program, the CMS will collect information on medical and pharmaceutical utilization in a large population that uses a great number of pharmaceuticals and has a high proportion of chronically ill patients (Platt and Ommaya, 2005).

Understanding the risk profile of a new drug requires an integrated and robust system for evaluating the premarket and postmarket risks. A current challenge in our understanding is that patients, health-care providers, and others assume that the most serious adverse effects are identified in premarketing studies; therefore, identification of new risks after widespread use raises concern about system failures (Mitchell, 2003). The true picture is that all drugs will develop new information concerning risks and benefits as they are used in the marketplace. The challenge is

identifying and balancing potential or actual risk with benefit as information develops over time.

The occurrence of ADEs and the role of consumers and health-care professionals in reporting these events prompted the Forum on Drug Discovery, Development, and Translation to convene a workshop to explore issues associated with reporting of ADEs and to identify actions to improve the drug safety system. The workshop addressed the following questions:

- How can ADEs be effectively identified, particularly when the adverse effects are rare?
- How can the direct, causal effects of drugs be distinguished from simple associations?
- How can health-care professionals and their patients aid in the identification of drug-related adverse events?
- How can knowledge of ADEs be more effectively used in clinical practice?

The workshop took place on November 3 and 4, 2005, in Washington, D.C., and was chaired by Jeffrey Drazen, MD, Editor-in-Chief of the *New England Journal of Medicine* and Professor of Medicine at Harvard Medical School. The reader is referred to Appendixes A and B for the workshop agenda and speaker biographies. Section 2 reviews current sources of information on adverse drug events, including the FDA's MedWatch program and the AERS, institutional review boards, and the CMS. Section 3 describes surveillance systems, surveillance technology, and data quality. Section 4 considers the ways that consumers and advocacy groups can be involved in reporting adverse events. Section 5 discusses drug interactions, problems with current databases for capturing and evaluating interactions, and difficulties in communicating information about adverse drug interactions. Section 6 describes new requirements for information contained on drug labels and how labels can be used to communicate information about risks and drug interactions to consumers and practitioners.

2

Current Adverse Event Reporting Systems

Participants discussed systems and structures currently in place for health-care providers, consumers, and others to report adverse drug events. Postmarket information on adverse drug events originates from patients and clinicians who are using and prescribing drugs. Reports of adverse drug events (ADEs) make their way to the FDA through various means—through pharmaceutical companies, which collect and report adverse events on their drugs; directly from providers and patients through the FDA's MedWatch system; from patient databases of payers such as the Centers for Medicare and Medicaid Services and managed care companies; and from hospitals. There are numerous challenges associated with the collection of ADE reports that may lead to significant underreporting of adverse events.

MONITORING ADVERSE DRUG EVENTS

In an effort to monitor the effects of drugs after their release into the market, the Food and Drug Administration (FDA) instituted the Adverse Event Reporting System (AERS) in 1993. AERS is a computerized information database designed to support the FDA's postmarketing safety surveillance program for all approved drug and therapeutic biologic products. AERS is supported by the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Staff members evaluate reports made by drug manufacturers, physicians, and consumers to detect safety signals and monitor drug safety. The report-

ing of adverse events provides a signal or hypothesis that may be further evaluated by epidemiological methods and forms the basis for further epidemiological studies when appropriate (FDA, 2005b). Manufacturers must report to the FDA the following serious and previously unknown adverse events within 15 days of their occurrence and conduct a follow-up investigation (FDA, 2005c):

- Events associated with drug use in a professional practice
- Events resulting from accidental or intentional overdose
- Events occurring from drug abuse
- Events occurring from drug withdrawal
- Any failure of expected pharmacological action

The analysis of serious adverse events identifies issues that should result in changes to drug labels or that require physician notification of adverse events. This information, as Anne Trontell, deputy director of the FDA's Office of Drug Safety, noted, allows the FDA, in collaboration with the manufacturer, to ensure that there is effective product labeling to alert health-care practitioners and patients to possible safety risks and areas of risk prevention.

Daniel Troy, a partner at Sidley Austin LLP and former chief counsel at the FDA, added that after a drug is approved by the FDA, manufacturers must submit quarterly reports for the first three years and annual reports after this three-year period. The FDA can extend the quarterly reporting period upon written notice. The content of reports includes a narrative summary, analysis of information in the 15-day alert reports, and a listing of actions taken since the last report, such as labeling changes or any studies that were initiated. The FDA can withdraw the approval of a drug if the correct reporting has not occurred.

The FDA does not conclude from a submitted report that a drug is the direct cause of an adverse event, but rather that the event is associated with use of the drug. The FDA does not impose on physicians any legal requirements for reporting adverse events because it lacks authority to regulate the practice of medicine, a responsibility of individual state governments. Currently, 20 states have mandatory reporting systems, but according to Mr. Troy his experience has been that there are known cases of adverse reactions that are not reported. In states without mandatory reporting systems, report submission is completely voluntary and therefore dependent on the participation of health-care professionals. Possible reasons for underreporting include the time it takes to complete a report, fear that reporting events will have a negative effect on the practice of medicine, and liability concerns. Mr. Troy recommended that the AERS be streamlined to encourage reporting, for example, a single-page form

that is tested with physicians. There should also be no liability faced by health-care providers who report adverse events.

MEDWATCH

The FDA's program for collecting data on ADEs is known as MedWatch. It has an outreach component, designed to facilitate public reporting of adverse events, and a reporting component, which provides the actual means for reporting, including an Internet portal for reporting drug event information. It also has standardized forms that can be downloaded and used to report ADEs (FDA, 2005d). In 2005, intake and acknowledgment of these reports were overseen by approximately five FDA staff who were assisted by contractors. Drug-related information that is collected through MedWatch ends up in the AERS if the adverse event is serious—i.e., if it results in a life-threatening event or hospitalization (or if it is for a new drug). The MedWatch system collects reports for other products as well—for example, medical devices and foods—and forwards those reports to the appropriate database.

The FDA reports that MedWatch captures only a small percentage of the total burden of adverse events (Trontell, 2004). Richard Platt of Harvard Medical School and Harvard Pilgrim Health Care stated that completing and filing forms for MedWatch (and the Vaccine Adverse Event Reporting System [VAERS]) requires clinicians to recognize that a medical problem may be an adverse reaction to a drug, remember how and where to obtain the forms, and then invest substantial time in providing the required information. These steps lead to substantial underreporting and incomplete reporting. In 2004, 48 percent of reports regarding adverse events were provided to the FDA through MedWatch by physicians and pharmacists (according to Trontell, predominantly pharmacists, with a lesser percentage from physicians) (see Figure 2-1). Consumers contributed only 17 percent.

Another concern about MedWatch is the variability of report quality. Although MedWatch is available to health-care professionals, these professionals are not necessarily taught how to use the system (Malenka et al., 2005). According to Mr. Troy, the FDA "generally assumes that only 1 in 10 adverse events is reported." However, utilization of other reporting methods, such as registries, can result in higher reporting rates. One issue with voluntary reporting is that clinicians report only when they think something is both significant and drug related. The large majority of adverse events are either not recognized or not reported, and there are unknown biases in the reporting that does occur, according to Dr. Platt. There have been suggestions that anonymity of reporting and perhaps

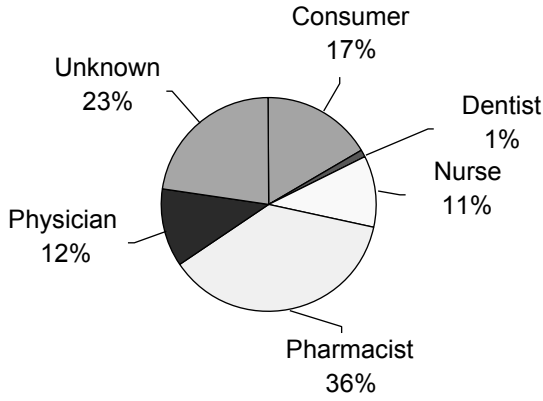

FIGURE 2-1 Sources of reports to MedWatch.
SOURCE: FDA (2005e).

overcoming the barrier of liability concerns would motivate people to file more adverse event reports, said Dr. Trontell.

Most adverse events are reported through spontaneous reporting that places a burden on health-care providers. The FDA budget is not adequate for the investment in information technology that could help with the collection of and access to quality data (Gottlieb, 2005). Information is becoming increasingly available in medical claims databases and clinical databases that could be used in reporting adverse drug events. According to Dr. Platt, "These databases provide relatively complete and unbiased information for many drug and vaccine exposures and for important outcomes, along with substantial comorbidity information. Databases are particularly useful when combined with review of the full-text medical records of a very small number of people to confirm the database information and to gather additional data."

REPORTING ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS

Current systems for reporting adverse events to institutional review boards (IRBs) are problematic because these reports rarely contain adequately detailed information and the data are reported sporadically and are not easily aggregated for analysis. In addition, the FDA has limited authority to regulate IRBs.

IRBs must review clinical investigations annually, at a minimum, and must maintain records of continuing review activities. According to Mr.

Troy, the FDA requires investigators to report an unanticipated problem to the IRB within 10 days. There are many reports received in a year that consist of raw and unanalyzed information. IRBs would be better served if information about agents used in a study was collated into summary reports. What is needed is a "manageable signal-to-noise ratio," said Mr. Troy, who further stated that without specific regulatory guidance in this environment, overreporting is the best option from the legal liability perspective. Bernard Schwetz, of the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (HHS) and a Forum member, echoed Mr. Troy's comments about reports to IRBs not being synthesized. OHRP has created a draft guidance document titled *Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others.* It is intended to assist IRBs, investigators, research institutions, HSS agencies that conduct or sponsor human subjects research, and other interested parties. OHRP believes that there will be more collaborative efforts by federal agencies that are involved in human subjects research to create a new approach to handling adverse events (HHS Office for Human Research Protections, 2005).

REPORTING ADVERSE EVENTS TO THE CENTERS FOR MEDICARE AND MEDICAID SERVICES

The Centers for Medicare and Medicaid Services (CMS) compiles medical data on patients it covers in order to manage reimbursement. The databases created are also used to collect safety data about medications and devices, although claims data must be validated with medical records. CMS has examined 65,000 charts. David Hunt of the CMS Quality Improvement Group reported that this chart review was initiated to detect errors in payment. However, it became apparent that these reviews could be used to monitor clinical events. A CMS program, the Medicare Patient Event Safety Monitoring System, will examine ADEs in the near future. The first adverse event areas to be assessed are those associated with two classes of drugs, anticoagulants and hypoglycemics; one specific drug, digoxin; and a specific class of reactions, antibiotic-associated diarrhea. These areas are also being examined by Medicare quality improvement organizations. Data are gathered from chart reviews based on a random sample of Medicare enrollees. Dr. Hunt stated that CMS plans to examine adverse drug events captured by Part D data as they relate to inpatients, because that existing mechanism already works reasonably well. Plans to examine outpatient data are under way, and CMS is working to promote electronic recording practices. Medicare part D data should provide important insight. However, it will take a few years before clean data from

Part D are available. CMS and the FDA will share this information, which will inform both organizations' quality improvement projects

CMS issued a guidance document in April 2005 supporting a system of postmarketing data collection for drugs for which national coverage decisions must be made under Medicare Part B (CMS, 2005). Reimbursement is a powerful driver for safety studies. Although Medicare will be collecting data on Part D drugs, it will have no authority to make coverage decisions based on that information (Gottlieb, 2005).

NEW APPROACHES FOR IMPROVING REPORTING SYSTEMS

Alastair Wood of Vanderbilt Medical School discussed new approaches to improve the current adverse event reporting systems. He described MedWatch and other reporting systems as being set up to detect rare events and said that what is needed is the capture of "high-frequency, high-impact" cases that are not detected with the current systems. "One approach," said Dr. Wood, "is to have incentives for long-term safety studies." This, however, would cause a long delay before drug approval and would not be cost-efficient. It would also entail discussion about which drugs would be subject to long-term study. Another approach is to conduct long-term safety studies after approval. This again requires consideration of which drugs would be chosen for study or whether all drugs should be studied.

One way to ensure the completion of safety studies is to offer extended exclusivity to companies that have acquired data to demonstrate that their drug is safe in the long term, offered Dr. Wood. This makes the drug more valuable to consumers and to the company. Most importantly, Dr. Wood said, "We need to move to a reward-based system that rewards demonstrated safety." In his proposal, drugs that lacked long-term safety data would be clearly identified as such. In this way, physicians could make the appropriate choice of medication with their patients. A fundamental issue would be the design of these safety studies, which under Dr. Wood's proposal would require FDA approval. In other words, extended exclusivity would be offered only for well-designed studies structured to answer important clinical questions.

Forum member Robert Califf proposed a clinical trial "light" system, in which new users of drugs would be notified about known drug risks and benefits. The system would indicate that the drug being prescribed had recently been approved but that information concerning both risks and benefits was being developed. Patients would be provided information to report any adverse events and asked to participate in follow-up studies concerning the medication.

3

Active Surveillance Systems

Active surveillance systems screen claims data and notify health-care providers who then determine if follow-up or adverse event reporting is required. These systems can scan for known adverse events or facilitate adverse event reporting. Analysis of claims data is required to examine suspected new adverse events or modulation in the frequency of common events. The frequency of events and the timing of the event associated with a particular drug will impact the surveillance system's detection ability (Brewer and Colditz, 1999). Currently no standard alert system is universally accessed and used.

Workshop participants discussed types of surveillance systems, current technology used by these systems, and challenges in obtaining quality data. According to Peter Kilbridge of Duke University, there is a great need for standard alert systems; however, the number of people working to build and connect such databases is relatively small. Each current approach usually focuses on the hospital or facility level. Historically, adverse drug event (ADE) surveillance has focused more on the inpatient than on the outpatient setting. A 2004 survey of hospitals in Missouri and Utah found that only 34.1 percent of these facilities reported implementation of computerized physician order entry systems for medications (Longo et al., 2005). The current emphasis in developing alert systems is on assessing drug interactions rather than adverse drug reactions.

TYPES OF SURVEILLANCE

Dr. Anne Trontell of the Food and Drug Administration (FDA) gave three examples of surveillance: drug-based, setting-based, and outcome-based. Drug-based surveillance occurs when clinicians prescribe a new drug product and actively report on patient safety. This approach examines populations of interest after the launch of a product. It is similar to the United Kingdom's prescription event monitoring system that follows the first 10,000 users of a new product. Japan's health-care system also engages in active surveillance in the first six months of a product's marketing. The UK and Japanese systems could serve as potential models for the United States in postmarketing surveillance.

Dr. Trontell discussed setting-based surveillance as another way to capture ADEs. Drug-associated adverse events may present or otherwise be concentrated in certain health-care facilities. Setting-based surveillance systems in hospitals, emergency room departments, or pharesis centers may help detect relevant drug-related events. Dr. Trontell also noted that the FDA, in collaboration with the Centers for Disease Control and Prevention (CDC), the Consumer Product Safety Commission (CPSC), and the National Electronic Injury Surveillance System (NEISS), looks at its ability to detect drug-related injuries that present to emergency departments.

The National Electronic Injury Surveillance System: Cooperative Adverse Drug Events Surveillance (NEISS-CADES) is a nationally representative subsample of 64 of 98 NEISS hospitals selected as a sample of U.S. hospitals (CDC, 2005). At each of the hospitals, coders review all emergency department charts for ADEs. The case definition excludes drug withdrawal, drug abuse, self-harm attempts, lack of therapeutic effect, and effects of medications administered in the emergency department. This system captures prescription and over-the-counter medications, vaccines, vitamins, and nutritional supplements.

The final area Dr. Trontell discussed was outcome-based surveillance of selected health outcomes that are often associated with drug toxicity. For example, the FDA is working with the Drug-Induced Liver Injury Network (a network of liver transplant centers) to solicit information about antecedent drug exposures in individuals who are listed for or require a liver transplant. Such a system may identify individual agents or combinations thereof that are associated with hepatotoxicity.

SURVEILLANCE TECHNOLOGY

Dr. Kilbridge reported that in the Duke University adverse event detection system, even with strong encouragement to report adverse events, approximately one out of every six events is logged into the

voluntary reporting system. In comparison, estimates are that the ratio in community hospitals is 1 in every 80 events. These data from Duke illustrate how voluntary reporting falls short of accurately reflecting the number of adverse events experienced by patients since 5 out of 6 events are missed.

Dr. Kilbridge pointed out that surveillance systems are constrained by the types of data available. Data are derived from many different sources and are highly variable in quality. He also indicated that the systems are resource intensive, consuming both financial and human capital. The low specificity of the alert system creates too many alerts for human staff to respond to each one. Dr. Kilbridge stated that the Duke system operates more than 60 triggers and sends the university hospital as many as 60 to 70 alerts per day, creating a substantial amount of work for health-care providers. Despite all this work, the system's current logic leads to a true alert only about one out of six times that such events occur. Dr. Kilbridge expressed the hope that rules can be developed with a high enough predictive value so that they can be effective as a real-time intervention. "We need to balance the opportunity for real-time intervention with the practicalities of the providers' work flow," said Kilbridge.

Dr. Kilbridge stated that while the Duke University Pharmacy Group made approximately 128 reports to MedWatch in the past year, it received 1,500 automated detected ADE reports and 4,000 voluntary reports from Duke University Hospital alone. Many of these adverse events were not necessarily reportable to the FDA. The majority of Duke's MedWatch reports originating in the pharmacy come from voluntary reporting by pharmacists who observe events they believe to be unusual. "We screen for things that we already know about as side effects of drugs," stated Dr. Kilbridge. Robert Califf commented that in the future, most active surveillance systems will automatically report both to the relevant pharmaceutical company and to MedWatch. However, he raised the question of whether the FDA would be able to handle the increased volume of reports.

Computerized data can be used to identify a signal that indicates the potential presence of an adverse event, and then human practitioners can intervene (Bates et al., 2003). Several claims-based systems and approaches that provide this information were discussed (i3 Drug Safety, Department of Veterans Affairs [VA], and the Health Maintenance Organization Research Network [HMORN]). According to the VA's Francesca Cunningham, these approaches have the benefit of understanding population characteristics as well as adverse events. Different recording systems track different patient information. All of this information must then be integrated to form complete health data for patients.

Arnold Chan of the Harvard School of Public Health emphasized the

need for an active surveillance system not only for drugs, but also for vaccines and devices. One advantage of active surveillance systems is that the data have both a numerator and a denominator, which allow confidence intervals to be placed around potential event rates, said Dr. Chan. There are several active surveillance projects under way. i3 Drug Safety developed a data system identifying all new drugs on the U.S. market since 2003. This information can be accessed when safety concerns arise and has been made available to the FDA by contract, said Dr. Chan. A pilot collaboration between the Critical Path Institute (C-Path) and community pharmacies established a pharmacy-based electronic registry of patients taking new drugs. This pilot project will gather and verify baseline information, then follow up with patients. However, there are many challenges to gathering useful information. As many as 29 percent of patients do not take their prescriptions, 40 percent take drugs not listed in their medical record, and a large percentage of ADEs are never recorded.

Health-care providers may track the incidence and nature of events among their patients for purposes of quality improvement. Computers search the clinical databases for telltale combinations of data suggestive of ADEs. However, these searches are constrained by the source, quality, and type of searchable data. Construction and maintenance of these systems is an expensive endeavor in terms of both time and resources. Hershel Jick of Boston University Medical Center and Forum member Garret FitzGerald of the University of Pennsylvania pointed out that the field of people qualified to use these data systems effectively is relatively small. Human capital is essential to the success of maintaining and utilizing any database, whether newly created or already in place. Trained and experienced researchers are vital components of the reporting system. Quick access to large pools of high-quality data resources that are required for quality research is also essential.

Micky Tripathi of the Massachusetts eHealth Collaborative emphasized the important role that technology plays in improving surveillance systems (see Figure 3-1). He stated that given current technology, the next step is to engage practitioners and patients in a meaningful way in order to involve patients in their own health care and information tracking. In his presentation, Dr. Tripathi discussed some of the limitations of paper chart reviews, citing in particular the difficulty and expense involved in gathering all relevant records and navigating through them to find pertinent case information. This creates a time lag between the occurrence of a drug event and the practitioner's ability to review medical data. One key benefit of computerized patient medical data is that they can be used to detect the frequency of adverse events and help identify methods to avoid them (Bates et al., 2003). Citing an example from an Indiana hospital, Dr. Tripathi stated that computerized surveillance systems detect

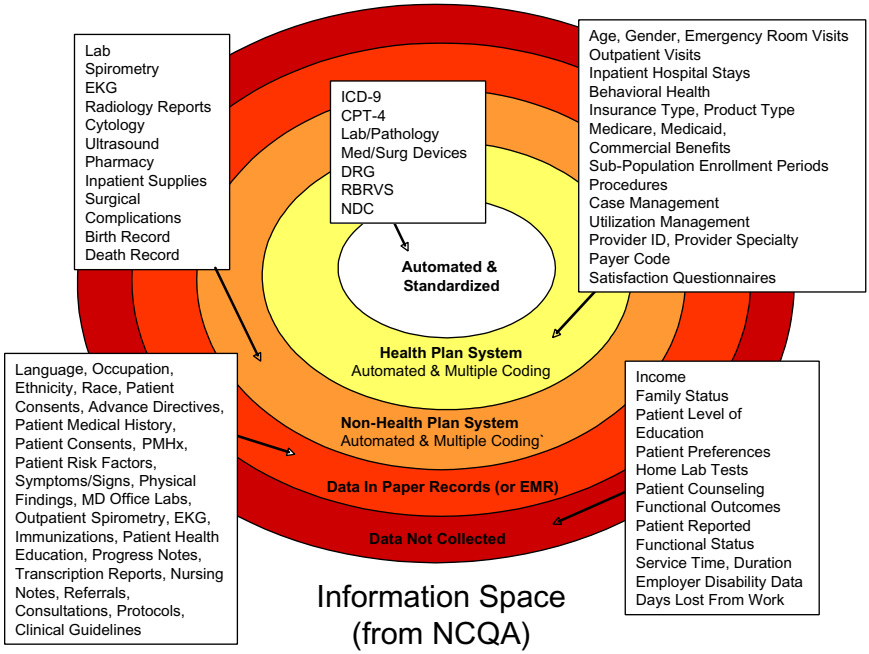

FIGURE 3-1 Levels of surveillance.
NOTE: CPT-4 = Current Procedural Terminology, 4th Edition; DRG = Diagnosis-Related Groups; EKG = electrocardiogram; ICD-9 = International Classification of Diseases, 9th Revision; NCQA = National Committeee for Quality Assurance; NDC = National Drug Code; RBRVS = Resource-Based Relative Value Scale.
SOURCE: Micky Tripathi, workshop presentation.

adverse drug event signals via the triggers found in patient medical records (see Table 3-1). As of 2004, 57.4 percent of hospitals surveyed used clinical codes from medical records to monitor patient safety, and 50.8 percent used quality improvement programs and discharge data to monitor patient injuries and adverse events (Longo et al., 2005).

Use of electronic medical records (EMRs) has developed in the health-care field in an effort to improve data quality and the efficiency of data acquisition. The development of EMR systems is often piecemeal and focused primarily on billing and revenue. Even when systems are in place they are not always fully utilized. The VA's EMR system is available free of charge but has not been widely adapted by other institutions. This is most likely due to challenges in integrating legacy systems and adaptation to varying institutional requirements. Implementation of EMR systems takes many years and requires substantial investments.

TABLE 3-1 Triggers in Patient Medical Records Used to Signal Adverse Events

Trigger	Example
Drugs used to treat events	Prednisone
Drugs known to interact with each other	Warfarin and antibiotics
Abnormal test or lack of laboratory tests conducted while the patient was taking a particular drug	Low platelet count
Physical symptoms associated with ADEs	Bleeding associated with use of NSAIDs

NOTE: NSAID = nonsteroidal anti-inflammatory drug.
SOURCE: Gurwitz et al. (2003); Micky Tripathi, workshop presentation.

According to Raymond Woosley of C-Path, an ideal surveillance database "should involve a hypothesis-based surveillance system, with accurate estimates of incidence. It should not only detect problems, but define the characteristics of adverse events, the associated risk factors, so we can identify methods of prevention." Patient demographics, baseline medical history, and drug history are all key points of information to be included in such a system. Pharmacy networks are an underutilized information resource. Dr. Woosley stated that "[pharmacies] are electronically better networked than anyone else in our health-care system." Dr. Woosley described a new research program at C-Path, an electronic registry into which pharmacies enter a patient's drug history, a drug list, and complete contraindication and drug interaction screening and then arrange for personal follow-up. The program recommends that patients also register with a drug information center, which has trained pharmacists who are able to record adverse event occurrences and recommend treatment for ADEs. These pharmacists would also be trained to record adverse clinical outcomes from medications and manage them effectively.

The use of common data languages when communicating drug information would facilitate this higher level of knowledge about the safety of drugs. Robert Powell of the FDA reported that the Clinical Data Interchange Standards Consortium (CDISC) was instituted to increase more effective communication. The CDISC is a nonprofit organization dedicated to developing industry-wide standards for gathering and storing electronic information (CDISC, 2006). However, Dr. Powell noted that developing data standards for communicating information does not

seem to be a priority for either government or industry. In the year 2000, authors of a CDISC white paper estimated that the annual cost to industry for transferring data was $122.5 billion (Kush, 2001). Dr. Powell suggested that accelerating the CDISC standard for data submission would facilitate better communication of safety information.

THE VETERANS AFFAIRS HEALTH-CARE DATABASE SYSTEM

The Computerized Patient Record System (CPRS) is a drug alert program embedded in the VA health-care system. It is a powerful resource for surveillance and adverse event evaluation. According to Francesca Cunningham of the VA, the VA health-care system has more than 7 million enrollees and tracks prescriptions for more than 4.9 million patients in approximately 150 medical centers, 800 outpatient clinics, and 135 nursing homes. Its ongoing information systems monitor the VA's population of high-risk patients. Elderly patients, patients with high medication use, patients exposed to new drugs shortly after approval, and patients with chronic health conditions are all at high risk for ADEs. Safety evaluations are routinely performed in which patients are categorized by demographic, medical history, medication, and treatment variables. They are then followed for 12 to 24 months. The system alerts providers to drug interactions, drug class duplications, and allergy warnings (Spina et al., 2005). The various databases can be integrated to give a more complete picture of the patient's medical history than any one of the databases alone. This pooled information can be used to identify and track adverse events.

Within the VA's database systems, the prescription database is merged with medical records, inpatient and outpatient files, and the mortality database. For specific projects, the VA has recently merged VA data with CMS databases for dual users, a move Dr. Cunningham reported helps the VA detect events that occur outside its own system. She provided a recent example of safety surveillance through the use of integrated VA databases. The VA found that the use of fluoroquinolones was associated with an elevated frequency of dysglycemia when compared to the use of azithromycin, particularly in diabetic populations. These findings led the VA to update the "VA Fluoroquinolone Criteria for Use," an educational document for physicians explaining the need to monitor for dysglycemias more closely in certain patient populations. An important next step for the VA's safety surveillance efforts will be to obtain provider feedback. "We want practitioner feedback. One of the things we are emphasizing is the evaluation of the impact that is made once this information is out," said Dr. Cunningham.

DATA QUALITY

Nancy Santanello of Merck Research Laboratories emphasized the importance of obtaining information about risk factors and confounding influences on ADEs before and during clinical trials. Postmarketing trials and observational studies need sufficient power and length of follow-up on real-life populations with realistic end points. Concerns about observational studies include lack of randomization, lack of collection of important information for confounding variables, and the impacts of unknown cofounders. Data may be incomplete, missing, poorly measured, or invalid. Data also can be biased. Nonrandomized groups may be unequal, and unmeasured characteristics may be different. Even when risk factors for a particular disease are well known, adjustments for comorbid factors in an observational study may not be sufficient to remove the bias caused by differences between the comparison groups resulting from unmeasured risk factors. Exposures and outcomes also can be misclassified. These are not independent, and the resultant outcomes may be strongly biased in either direction even if the misclassification is nondifferential. Dr. Chan added that there is a need for studies to address comorbidity and comedication use in real-life populations in order to improve postmarketing safety surveillance. Dr. Santello commented that "although a paradigm for the assessment of causality using observational studies exists, it must be applied cautiously and deliberately before definitive conclusions can be drawn." She concluded that well-designed observational studies can supplement clinical trials and provide important additional information concerning the safety and effectiveness of therapeutic interventions.

Dr. Powell called for a more quantitative approach to the development of protocols and a higher level of learning throughout the entire development process. He noted that characterizing adverse events in terms of the time of onset, the relationship to when the dose is given, and how long it takes the adverse event to end is important. Unfortunately, this information is not found in many protocols. As a logical next step to resolve these issues, Dr. Powell recommended discussing safety and efficacy in the early stages of protocol development.

4

Consumer Involvement in Reporting Adverse Events

Recent Food and Drug Administration (FDA) recalls have adversely affected public perception of the pharmaceutical industry and the system for regulating drug safety. According to a 2005 poll of consumers, 43 percent of surveyed adults felt that the pharmaceutical industry did a "bad job" serving its consumers (Supermarkets, 2005). Although consumers have a great incentive to report adverse events, there are few efforts to engage them more actively in the process, and there is no comprehensive system in place for consumer reporting of adverse events in an outpatient setting. Workshop participants emphasized the need for increased consumer and advocate involvement in reporting events and ways in which this can be achieved. According to Forum member Michael Katz, who presented on behalf of the International Myeloma Foundation (IMF), advocacy organizations can take the initiative to quickly deliver meaningful drug safety data. The IMF began receiving anecdotal reports through its hotlines and e-mail list about elevated creatine levels associated with the use of zoledromic acid. Zoledromic acid had been approved for use in the prevention of bone mineral loss in a variety of specific clinical settings when administered by a 15-minute infusion; there was no warning about potential kidney toxicity in the label, but experience suggested that this could exist if proper infusion approaches were not used. The IMF helped advise patients about safe use of the medication based on clinical experience and the problem diminished. "In fact, the manufacturer is now publishing studies showing that there is now no elevated

kidney toxicity risk. In all likelihood, this is a direct result of the change in clinical practice," Mr. Katz said.

In 2004, IMF again became involved in patient education about potential adverse events associated with zoledromic acid after receiving notice of a high incidence of osteonecrosis of the jaw in patients taking the drug. A web-based survey of myeloma and breast cancer patients conducted in July 2004 by the IMF identified a time-dependent risk related to the drug (Durie et al., 2005).

Public education programs that raise public awareness and communicate tangible public benefit of improved adverse reporting systems are ways in which patient advocacy groups and even patients themselves can play a role in reducing adverse drug events (ADEs). The development of an improved infrastructure for consumer reporting will benefit from the increased input of those that the system was designed to serve.

CONSUMER INVOLVEMENT IN THE CURRENT MEDWATCH SYSTEM

MedWatch captures only a fraction of the adverse events that occur, leaving the total burden unknown. Alison Rein of the National Consumers League concluded that this is due, in part, to a lack of meaningful consumer engagement in this process and the fact that reporting mechanisms are divorced from routine practice. Dr. Marvin Lipman of Consumers Union stated: "For consumers to play a role, they need to be made aware of the importance of reporting adverse drug effects, not only to their physician and pharmacist, but also to a central body, the FDA." Ms. Rein reported that MedWatch is not on the radar of most consumers and is not integrated into the health-care delivery system. She compared patient reporting within the current MedWatch system to the United Kingdom's new yellow card system (see Table 4-1). This system is managed by the Medicines and Healthcare Products Regulatory Agency (MHRA) and performs safety surveillance. Each report, which is actually a yellow card, is acknowledged and registered upon receipt and then entered into MHRA's Adverse Drug Reactions Database. Reports are assessed by health-care professionals in the Pharmacovigilance Group of the MHRA Post Licensing Division. This assessment includes the use of data from other sources such as pre- and postclinical trials, case reports in the medical literature, data from other drug regulatory agencies, epidemiological studies, and record linkage databases. The Committee on Safety of Medicines and its Subcommittee on Pharmacovigilance advise MHRA on potential safety issues and appropriate regulatory actions.

The yellow card system allows consumers to report online, by prepaid mail, and by phone. Translation services are available for those who are

TABLE 4-1 Comparison of Consumer Reporting Systems

MedWatch	Yellow Card
Available online, via mail, or by phone	Available online, by phone (translation), via mail (no postage), or in almost any relevant care delivery setting
Encourages physician completion of form; no separate form for consumers	Encourages consumer completion of form; separate, user-friendly form for consumer use
Does not actively seek reporting of events related to OTC medications, vitamins, and herbal supplements	Seeks reports of events related to OTC medications, vitamins, and herbal supplements
Collects fewer fields; insufficient for desired analyses	Collects more and better data

NOTE: OTC = over-the-counter.
SOURCE: Rachel Behrman, workshop presentation.

not proficient in English and thus may have difficulty completing the forms. Although MedWatch also can be accessed by the Internet, mail upon request, or telephone, Ms. Rein reported that when she tried to use the 1-800 number provided to consumers, she found the service difficult to navigate. She noted in particular that the terminology used on written forms and by the telephone service is above the level of health literacy of the average consumer with no medical background.

The yellow card system actively seeks reports of events associated with over-the-counter medications, vitamins, and herbal supplements in addition to prescribed medications, while the MedWatch system deals only with prescription drugs. Ms. Rein pointed out that the yellow card form is designed for consumers, not just for health-care professionals. However, the MHRA recommends that consumer reports be validated by a health-care professional (MHRA, 2005). Ms. Rein reported that the system can be accessed in some form in almost any relevant care delivery setting, such as pharmacies and physician offices. She viewed the yellow card's user-friendliness and wide availability as encouraging patients to engage in safety surveillance by completing the form on their own. With MedWatch, there is no consumer interface, and all users receive the same form. The system encourages physicians to complete the written forms by instructing patients to fill the form out with their doctor. Ms. Rein sees this as discouraging patients from completing the forms themselves.

The MedWatch system collects data in fewer fields than the yellow card system. Ms. Rein believes that it would be helpful in MedWatch to have more data initially available and have the ability to narrow down

as analysis dictates, rather than collecting too few data to be able to run a desired analysis.

The MedWatch program in its current form has several challenges as also noted by Dr. Lipman. Its minimal staff is responsible for capturing events associated not only with drugs, but with devices as well. MedWatch is also set up to focus on potentially lethal events, not the more frequent minor events that can still significantly decrease patients' quality of life. Minor events are not dismissed, but they are not the focus of analysis. A key to making the system more functional will be to define which data are most useful and to determine how best to engage consumers.

OUTREACH PROGRAMS AND TOOLS

Dr. Lipman reported that adverse events are estimated to occur in as many as 20 percent of patients taking medications, totaling more than 4 million events per year. Many adverse events are not life threatening, but they may cause serious physical or mental distress. Dr. Lipman noted that consumers are the individuals who are most motivated to report adverse events, because they have the most at stake. Engaging consumers to work with their health-care providers would be an important way to "connect the dots" and make sure all necessary information is transmitted to the FDA. As Mr. Katz pointed out, patients have as much to lose by misinformation as by oversensitivity to drug safety. "It's very scary to think about adverse events that could happen to you as a patient. But when you're in a space with an incurable disease . . . it's even scarier to think that drugs will be taken off the market on a wholesale basis, or that it will be harder to gain approval for new drugs that could help people," he added.

Engaging patients can result in a much richer understanding of drug effects. The cause of a poor health outcome is difficult to determine. Where does the course of the disease end, and where do the effects of the drug begin? The system for detecting adverse events is full of noise, and sometimes a true signal is difficult to discern. Patient advocates and the FDA could work together to eliminate some of this noise. A role for advocacy groups would be to provide reporting assistance and help patients understand what should be reported, said Karen Cox of University of Missouri Health Care. Dr. Cox discussed how consumers interact with the University of Missouri Health Care system. She indicated that consumers have been successful in using the online health system web page to enter their compliments or complaints.

Mr. Katz called for the development of outreach programs for patients to share their collective experiences with each other and with those who develop health-care policy. Consumer groups and patient advocacy organizations have begun to take steps toward providing consumers with

more information about drugs and their potential adverse effects. Dr. Lipman cited a public outreach project launched by Consumers Union in 2004 as a step toward providing consumers with reliable information about drug safety. Consumers Union initiated the Best Buy Drugs website (www.crbestbuydrugs.org) to educate consumers about their medications, specifically the drugs that give the best value. The website consists of monographs examining ACE (angiotensin-converting enzyme) inhibitors, antidepressants, antihistamines, drugs for attention deficit hyperactivity disorder, beta-blockers, calcium channel blockers, proton pump inhibitors, and nonsteroidal anti-inflammatories. The monographs follow the methodology of the Oregon state program—the Drug Effectiveness Review Project. Fourteen state Medicaid programs have adopted these reviews. The website also provides information about diseases and disorders and common side effects for drugs in each class.

The Internet has provided a very powerful tool for consumers to find and share information via e-mail lists, support groups, and networking. The Consumer Reports website (www.consumerreports.org) alone has more than 2 million active subscribers, said Dr. Lipman. The greatest strength of the Internet as a communication vehicle is that it is a free medium that many people can access easily. Dr. Cox reported that University of Missouri Health Care receives 24 percent of its patient compliments and complaints via the Internet (with no advertising) (see Figure 4-1). In addition to the Internet, patient-initiated reports come from a variety of different sources such as phone calls, letters, e-mails, and patient satisfaction surveys.

POSTMARKETING SURVEILLANCE AND DIRECT-TO-CONSUMER ADVERTISING

Mr. Katz provided a description of the drug approval system (see Figure 4-2). In the preapproval stage, drugs are assumed to be harmful until they are proven safe at reasonable dosages. However, there is a paradigm shift in the way drug safety is considered after approval: drugs are assumed safe once approved. Drug companies have limited incentives to conduct postmarketing safety studies because evidence against a product would necessitate labeling changes or even withdrawal from the market. In Mr. Katz's opinion, the current spontaneous reporting-based system is too slow to be relied upon for accurate, up-to-date postmarketing safety surveillance.

Direct-to-consumer (DTC) advertising continues to play an influential role in consumers' medication use. It can stimulate consumers' discussion with physicians regarding medical conditions, but it can also elevate the use of products in circumstances that could be inappropriate. There

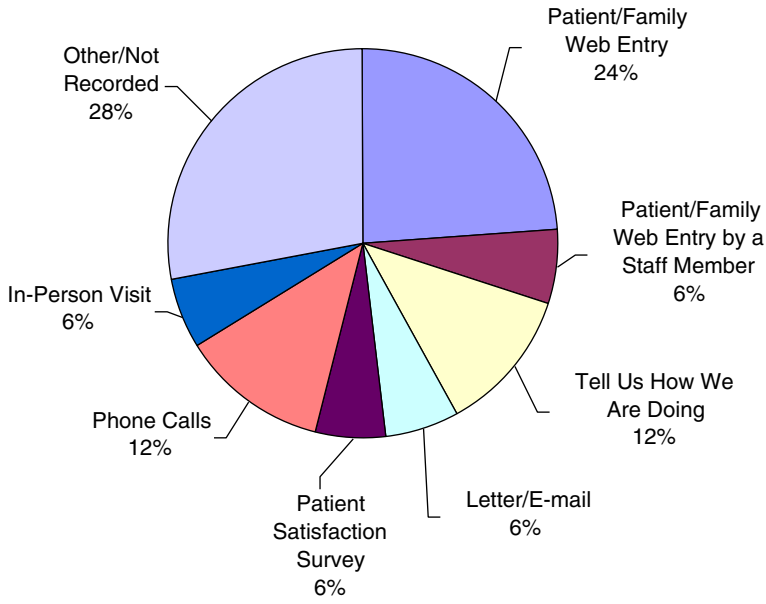

FIGURE 4-1 Patient-initiated comments (compliments and complaints) by source in University of Missouri Health Care (n = 6,661 over 45 months).
SOURCE: Karen Cox, workshop presentation.

has been widespread discussion about tighter regulation of the content of these ads. Currently, the United States is the only country other than New Zealand that allows them. Mr. Katz noted that DTC ads should contain reference to a consumer portal, such as MedWatch, for adverse event reporting.

ROLE OF ADVOCACY GROUPS

Advocacy groups can represent an intermediary between the public and the research community. They can work with clinicians and scientists to identify drug risks and preemptively address them by promoting safer drugs. Advocates can also use their networking capabilities to get information out to the public. To improve consumer involvement in reporting adverse events, advocacy groups could direct their resources to consumer education. Dr. Lipman recommended that mechanisms for the delivery of educational content could consist of point-of-sale drug information leaflets, consumer representatives or FDA advisory panels, and a clinical trials registry system that reports both positive and negative results of

FIGURE 4-2 Comparing pre- and postmarketing paradigms.
SOURCE: Michael Katz, workshop presentation.

drug studies. Marketing success stories of change driven by consumer reports may boost consumer confidence in the regulatory and safety surveillance system.

Advocacy group participation would help protect particularly vulnerable patient populations, such as young children and the elderly. More than twice as many prescriptions were filled for those 65 and older (23.5 prescriptions per year) than for those younger than 65 (10.1 prescriptions per year) (Stagnitti, 2004). A greater number of medications taken by a patient increases the likelihood of an adverse event occurring. There has been concern that drugs for seniors are often not appropriately prescribed. One study found that as many as 21.3 percent of community-dwelling patients 65 years or older were using at least one inappropriately prescribed drug (Liu and Christensen, 2002). Inappropriate prescribing of drugs in this age group, specifically for women, has led to concern for patient safety and appropriate utilization of health-care resources. In light of the recent concern about an increased risk of cardiovascular events associated with the cyclooxygenase-2 (COX-2) inhibitor drugs, studies showing an increase in the prescribing of COX-2 drugs for patients who would be appropri-

ate candidates for nonsteroidal anti-inflammatory drugs are especially relevant (Goulding, 2004). The issue of over- or underprescribing medications for the elderly requires greater scrutiny in order to prevent potential adverse events and to promote better health and appropriate utilization of health-care resources.

POTENTIAL SOLUTIONS AND NEXT STEPS

Solutions to reporting issues may not necessarily have to be high tech and can build upon existing mechanisms for reporting. Ms. Rein suggested looking to successful reporting programs, such as the United Kingdom's yellow card system, for models of how to provide consumers with multiple avenues for reporting. Ms. Rein believed that the MedWatch system needs to be improved but is still a valuable surveillance tool. "We need to work to improve visibility of MedWatch by integrating reporting into the health-care delivery system," she said. Ms. Rein suggested public service announcements and direct-to-consumer advertising as possible ways to increase MedWatch visibility, as well as distributing the form (and/or access information) to patients in relevant clinical care settings. User accessibility could be improved by establishing separate web and telephone interfaces to provide consumers with multiple avenues for reporting events. Beyond MedWatch, Ms. Rein indicated that adverse event reporting should be a central element in electronic prescribing and medication management systems. Other avenues include technical support for training in ADE recognition and reporting and reimbursement policies that create incentives for ADE reporting; communication channels between doctors and patients and between patients and the FDA could be enhanced. Electronic resources could be further developed for disseminating safety and reporting information.

Dr. Lipman suggested next steps that would benefit consumers. The first is the formation of a drug safety oversight board with its own regulatory power, comprising consumer representatives and scientists with no industry ties or involvement in the approval process. Second, a clinical trials registry should be established and monitored. Both positive and negative trial results should be posted in a public forum. Third, DTC ads could be regulated with respect to content and subject to a two- to three-year moratorium after a drug is marketed. "To counter pharmaceutical ads, the FDA itself could launch a program of public service advertisements about drug safety, adverse drug reaction reporting, and the importance of postmarketing surveillance," said Dr. Lipman.

5

Drug-Drug Interactions

In addition to adverse events caused by use of a single drug, adverse events can be caused by drug interactions. Drug-drug interactions (DDIs) can make a medication less effective, cause unexpected side effects, or increase the action of a particular drug (FDA, 2003). They have the potential to cause significant harm to patients. Workshop participants discussed databases for recording and evaluating DDIs and ways to effectively communicate information about DDIs to practitioners and the public.

Sidney Kahn of Pharmacovigilance and Risk Management, Inc., noted that all drugs have actions that we do not fully understand. Robert Califf, Forum member, added that it is hard to define exactly what characterizes an interaction. He asserted that more research is needed to help health-care providers make more informed decisions about how interactions occur and which ones are clinically significant. DDIs can be neutral, synergistic, or additive.

Preventing medication errors and making appropriate decisions about prescribing drugs for patients who are taking multiple medications will reduce adverse drug events (ADEs). In one study, 6.5 percent of pharmacist-screened admissions to a unit of a hospital's medical service were drug related, and 67 percent of those cases were considered to be preventable (Howard et al., 2003). In a systematic review of 15 investigations, an earlier study found that a median of 7.1 percent of hospital admissions were drug related and 59 percent of those cases were preventable (Winterstein et al., 2002). The drugs most commonly associated with

preventable drug-related admissions are nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, beta-blockers, antiepileptics, diuretics, sulfonylureas, digoxin, inhaled corticosteroids, nitrates, and insulin (Howard et al., 2003). From a purely financial perspective, improving databases that monitor drug interactions is advantageous. Zynx Health representative Scott Weingarten asserted that a perfect drug information database could potentially save the U.S. health-care system $4.5 billion per year (Hillestad et al., 2005).

DRUG INTERACTION DATABASES

Although health-care systems have a structural framework in place for capturing and evaluating DDIs (see Figure 5-1), there are several problems with current information-capture systems. Multiple drug compendia exist, including Clinical Pharmacology Online, *Drug Interaction Facts*, and First Databank. However, these different systems often disagree on which

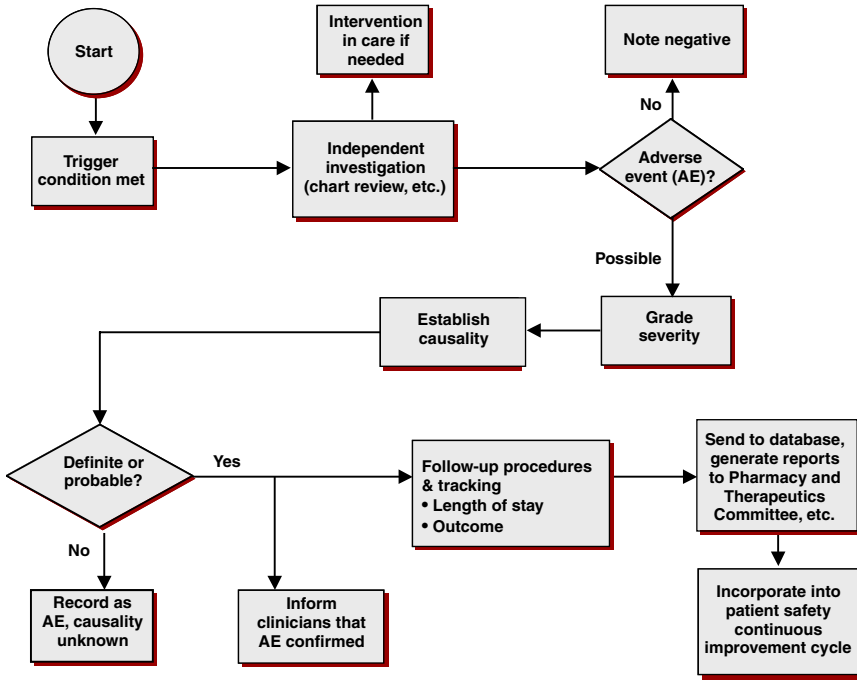

FIGURE 5-1 Adverse drug event surveillance: evaluation process in the Duke University Health System.
SOURCE: Peter Kilbridge, workshop presentation.

interactions having the greatest clinical importance, noted Jacob Abarca of the University of Arizona, College of Pharmacy.

A recent analysis conducted by Dr. Abarca noted limited agreement among drug-drug interactions considered to be of highest clinical importance (i.e., "major" drug-drug interactions) (Abarca et al., 2004). Four commonly used drug interaction compendia were chosen for the analysis: *Evaluations of Drug Interactions* (2001), *Drug Interaction Facts* (Mangini, 2001), *Drug Interactions: Analysis and Management* (Hansten and Horn, 2001), and the DRUG-REAX program (Moore et al., 2001). The analysis found 406 DDIs that were classified as being of highest clinical importance in at least one of these references. Only 2 percent were listed in all four compendia. The interclass correlation coefficient was 0.09, indicating very low agreement on the classification of major drug-drug interactions.

Russell Teagarden of Medco Health Solutions, Inc., recommended the establishment of uniform criteria for interactions and adverse drug reactions to reduce variability in defining what constitutes a major interaction. Mr. Teagarden, who contributed to *Drug Interaction Facts* (Mangini, 2001), pointed out that there is variability not only among sources but often within the groups working on each individual source as well. He reported that existing databases are not integrated, so clinically important information does not come from a single, easily accessed system. Establishing uniform criteria for drug interactions and adverse drug reactions may address robustness and concordance issues among information sources.

Dr. Kahn noted that a standardized terminology to uniformly evaluate interactions for their clinical importance is a necessity, "because if you can't describe it, then you can't analyze it." Variable data quality makes a large portion of the collected knowledge unusable. Although databases can alert doctors and pharmacists to dangerous interactions, health-care providers are unable to respond to every alarm while still performing their clinical duties. Physicians can become subject to alert fatigue, which can cause notifications to be bypassed or switched off. Dr. Weingarten noted that some systems are overly sensitive, leading to many alarms; this leads to alert fatigue and decreased pharmacist productivity. The use of computerized systems creates an opportunity to issue alerts for potential DDIs. However, these alerts are embedded within other drug alerts that can make DDIs easy to ignore. Up to 88 percent of all drug alerts are overridden by community pharmacists (Chui and Rupp, 2000), said Dr. Abarca, and only one in nine alerts was deemed useful by providers, according to a 2005 study (Spina et al., 2005). "I think if we sent an alert to a pharmacy that said, 'Your pharmacy is going to explode in 5 seconds,' they would just override it and move on to the next prescription," said Mr. Teagarden. However, pharmacists and providers consider DDI alerts more useful than other types of drug alerts (Abarca et al., 2006).

Mr. Teagarden and Dr. Weingarten agreed that pharmacists feel that the alerts are overly sensitive and not specific enough. To prevent physicians and pharmacists from being conditioned to ignore alerts, Dr. Abarca recommends that criteria be established for when to activate point-of-service alerts. "You could have the best, most comprehensive, most sensitive drug database in the world, but if it is turned off, it is not going to help patients," said Weingarten. Stuart Levine of the Institute for Safe Medication Practices shared the results of two pharmacy system surveys conducted in 1999 and 2005. In the six-year period, very little changed in databases and information systems. In fact, said Dr. Levine, many systems showed a decrease in alert effectiveness.

Pharmacy benefit managers (PBMs) electronically share information about drugs with health-care providers, manufacturers, and heath plan sponsors. These linked databases could potentially provide valuable information about reducing harm from inefficacy, drug interactions, and adverse drug reactions. Mr. Teagarden explained that PBMs have a general interest in protecting patients from drug interactions and adverse events. In addition, smarter coverage decisions can be made from more robust and high-quality data. Mr. Teagarden expressed hope that technological advances in data storage will help PBMs take a greater role in preventing DDIs. However, he recommended that criteria should be established for alerting various stakeholders about drug interactions and adverse drug reactions.

Information about interactions can help plan sponsors decide what drugs they want to cover and where in the prescription formulary they should reside. Analysis of prescription claims data from a major PBM showed that 374,000 out of 46 million participants had been exposed to a potential drug interaction of clinical importance (Malone et al., 2005). Because coverage decisions are effected the same day a drug is placed on the market, noted Mr. Teagarden, any drug interaction database needs to be maintained and updated rapidly as patients are exposed to new products. Medco has found that plan sponsors also expect new information about existing drugs to be accessible and updated in a timely manner.

The potential for collaboration among PBMs, plan sponsors, and retail pharmacy networks could result in the development of a new, single database of interaction information. Even if such a product were used only for educational purposes, the groundwork for interinstitutional information sharing needs to be addressed. Mr. Teagarden expressed hope that the surveillance criteria established would detect adverse events and interactions earlier and also utilize prescribing information to detect drug interactions. "We might be able to pick up on something early whether it is identifying drugs expected to be used to treat an adverse reaction, or looking at prescribing patterns to detect drug interactions," he said.

Mr. Teagarden acknowledged that the current systems and approaches between PBMs and retail pharmacy networks make this challenging. However with roughly 57,000 retail pharmacies making up one single network, added Mr. Teagarden, a significant volume of information is available.

COMMUNICATING DRUG INTERACTION INFORMATION

Patient education is an important step in the reduction of DDIs. For example, one Australian study found that education for physicians that was focused on better use of prescribed NSAIDS reduced the rate of hospital admissions for upper gastrointestinal bleeds by 70 percent (May et al., 1999). The more drugs a patient takes, the more likely is a DDI to occur. Some of the detailed scientific information from drug interaction studies is available to the public through the New Drug Application, which can be obtained through the Freedom of Information Act. However, not all information is disclosed in the public domain due to intellectual property and liability concerns of industry (Kraft and Waldman, 2001). Dr. Kahn stated, "There needs to be some kind of published database that is available to prescribers and the general public that actually contains real information on prioritization and frequency of potential interactions." Dr. Abarca indicated that he did not know of any DDI information specifically for consumers available on the web. However, he discussed a University of Arizona project that developed a list of 16 websites that all met informal criteria for providing helpful information that is reviewed and obtained from independent sources. However, Dr. Weingarten pointed out that the content of these websites varies tremendously. "Some information is accurate and easy to understand, some is accurate and very difficult to understand without a medical background, and some information is just plain wrong," he said.

The Internet is a powerful communication tool, capable of reaching large numbers of people while generating little overhead expense, but the many sources of information on the Internet offer inconsistent and sometimes inaccurate information about the dangers associated with drugs. On the other hand, this diversity prevents any one source from dominating the information available to consumers, regardless of its accuracy. The Federal Trade Commission (FTC) could intervene if the market share of one particular drug information company became too large. Such government action took place when Medi-Span (owned by J. B. Laughery, Inc.) and First Databank merged in 1988. The FTC sued the Hearst Corporation, parent of First Databank, under charges that First Databank was using monopoly power to increase prices for customers who used its drug

information database (Lowe and Krulic, 2005). Hearst paid $19 million in settlement and divested Medi-Span (FTC, 2001).

Dr. Kahn proposed that a cross-disciplinary DDI working group be formed to create improved tools for communicating interactions and consequences. He believed that this group could identify and prioritize DDIs, develop a public database capable of receiving all new labeling information on drug interactions, perform an ongoing review of data from the FDA and the published literature, and possibly recommend specific interaction studies. He indicated that a model for the formation of such a group could be found in the National Coordinating Council for Medication Error Reporting and Prevention, an independent partnership of health-care organizations with the goal of reducing medical errors.

6

Drug Labels

The drug label serves as an important source of information for physicians when making prescribing decisions (Ray and Stein, 2006). There are, however, concerns about the usefulness of information contained in drug labels. Leander Fontaine of Pharmiceutics LLC noted that the drug label uses precisely defined regulatory terms such as *adverse events* or *adverse reactions* that might not be interpreted correctly by physicians and patients. Ed Staffa of the National Association of Chain Drug Stores stated that pharmacists worry that they will miss major drug interactions by having to sift through all the minor or theoretical ones. As an example of the volume and impracticality of this information, in the year 2000 edition of the *Physician's Desk Reference*, the entry for cisapride occupied more than 10 pages and contained more than 470 facts about the drug (Woosley, 2000).

Furthermore, changes to labels and black boxes often do not occur in a timely fashion. One study found that only 50 percent of new adverse drug reactions are documented in the *Physicians Desk Reference* within a seven-year period (Lasser et al., 2002). "Labeling, by itself, although it is considered a principal tool for communicating drug information, generally does poorly. The FDA guidance for revising labeling goes some way toward improving the process, but not far enough," said Sidney Kahn of Pharmacovigilance & Risk Management, Inc. According to Dr. Kahn, labeling information should be available, up-to-date, and easy to navigate and should contain trusted information about suspected adverse reactions.

The greatest problem in drug labeling is how to improve the quality of the data presented to the prescriber, particularly information concerning drug-drug interactions. Currently, the information available is not helpful in managing patients in real time, and drug interactions are found only on newer product labels, not the older ones, said Dr. Kahn.

In the present regulatory environment, all possible adverse reactions are included on labeling because exclusion of information could potentially represent great legal liability. "There is a common misconception that FDA regulations require that every single potential adverse reaction report be listed on the label, but that is not the case." said Rachel Behrman of the FDA. Processing excess information is an inconvenience experienced not only by prescribers. The burden of so much content impacts pharmacists as well. "Part of the reason for the information overload in pharmacies sometimes is the concern of the pharmacy owner or operator hearing that if they don't let the pharmacists see all of the information, all of the potential interactions, all of the theoretical interactions, that they will somehow be held liable for missing something down the road," said Dr. Staffa.

NEW LABEL REQUIREMENTS

The FDA estimates that 300,000 preventable adverse events occur each year in the United States because of confusing medical information (FDA, 2006). The development of content for the label is a result of collaboration among the FDA, industry, and U.S. Pharmacopeia (USP) standards. Although companies write label drafts, only the FDA has authority over the final content. After approval, a label change can be requested by the FDA, but the company is not required by law to comply (Ray and Stein, 2006), although the FDA does have absolute authority to withdraw the drug.

To address concerns about labeling, the FDA has recently changed the format of drug labels in an attempt to make the information more useful. The new labels have a brief highlights section (see Figure 6-1) that summarizes information contained in the boxed warning, indications and usage, and dosage and administration. It also refers the health-care professional to the appropriate section of the full prescribing information (FDA, 2006).

Manufacturers must add any new information learned in the preceding year to the highlights section in an effort to keep physicians updated on new indications and interactions. A toll-free number and Internet address will be provided on the label to make reporting incidents more convenient. A table of contents and the date of initial drug approval will also appear on the product labeling. As of December 2006, all marketed

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON¤ (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

----------INDICATIONS AND USAGE ----------

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION ----------

- Stroke: 50 mg once daily with food (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS ----------

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch/report.htm*

----------DRUG INTERACTIONS----------

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

FIGURE 6-1 New drug label format.
SOURCE: Rachel Behrman, workshop presentation.

prescription drugs had to have electronic copies of their labels on the Medline website and be accessible free of charge. This information is to be kept up-to-date within 24 hours of approval or the FDA's receipt of information, added Dr. Behrman. Up-to-date information on the FDA labeling initiative can be found at http://www.fda.gov/cder/regulatory/physLABEL/default.htm.

COMMUNICATION OF RISK TO CONSUMERS AND PHYSICIANS

Drug labels do not communicate the likelihood that a particular adverse event will occur when taking the drug. Dr. Fontaine suggested there should be approaches to inform consumers and physicians about the level of causal certainty in labeling, as well as severity or relevance categories of adverse reactions based on their expected probability, when this information can be obtained. He proposed that the adverse reactions section of U.S. labeling provide only lists of (suspected) adverse reactions (i.e., a causal relationship between product use and type of event is considered at least a reasonable possibility). Tables of mere adverse events from clinical trials, to the extent they are considered valuable information for prescribers, should be provided in a scientific background document to the labeling, comparable to the scientific section of Canadian drug labels.

Dr. Fontaine proposed that labeling inform consumers and physicians about the level of causal certainty of suspected adverse reactions. The likelihood that an adverse reaction will occur when taking a drug should, he suggested, be illustrated both by listing reporting rates of adverse events observed in clinical studies (as it is done currently) and by grouping reactions in frequency categories based on an estimate of attributable risk (applying the methodology used in the European Union); the latter would provide value-added, relevant information for the authors of patient information texts. To make risk communication effective, the medical and scientific community, users, media, industry, and regulators must have a common understanding and acceptance of the decision-making principles behind risk labeling; must agree on the meaning of terms such as *adverse reaction*, *adverse event*, and *risk*; and must use such terminology transparently and with discipline.

Dr. Fontaine also noted that to ensure that labeling is the primary trusted source of information about the risk of a product, any addition of new adverse reactions and interactions should be accompanied by a public summary of the evidence that supports the new information and by a discussion of the level of uncertainty about a causal association (see Figure 6-2). "The information consumers need should be from a single source

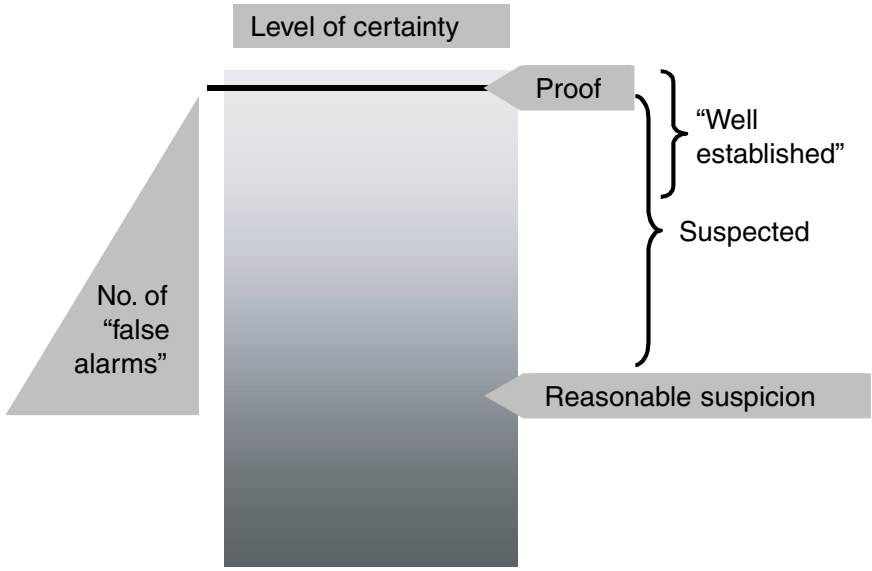

FIGURE 6-2 Level of certainty in association between a drug and an adverse event.
SOURCE: Leander Fontaine, workshop presentation.

and uniform in content for each drug or drug class. It should include all the information necessary for optimum drug use," said Dr. Lipman.

DRUG LABELING AND DRUG-DRUG INTERACTIONS

Labels are not being utilized effectively to communicate a drug's potential side effects or interactions with other substances. "We need to think about putting information in formats that are more clinically directed and useful, although a way of testing such formats . . . has yet to be established," said Jeffrey Drazen. Dr. Kahn added that it is extremely necessary to devise a categorization or standard terminology to uniformly evaluate interactions for their clinical importance. He noted that the FDA and industry are restricted by the liability concerns surrounding labeling. As discussed earlier, parties have incentives to cite every possible safety hazard associated with drug use, resulting in too much information on the label for it to be useful. All reported safety information must be included on the label because there is no framework for excluding it. "Correct and accurate is good and is not good enough. Information has to be actionable," stated Dr. Kahn in reference to information included on drug labels.

He added, "The end result is that information that is currently available does not help prescribers in the management of patients in real time."

Since DDIs involve at least two drugs, interaction information may be placed on the label for the newer product in an interactive pair, but not for the older drug. The side effects listed on the label give no indication that the likelihood of experiencing these symptoms was higher when taking the drug or the placebo. Robert Califf emphasized the need for a third party (neither the FDA nor the pharmaceutical industry) to decide what information is relevant to consumers and useful to prescribers and therefore should be included in labeling. "I wouldn't want the label content to be either a market-driven issue or an opinion poll," said Dr. Califf.

Mr. Teagarden proposed the United States Pharmacopeia (USP) as a good medium for developing an official list of drug interactions derived from its official monograph for content. USP has already defined medication error through its National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). USP founded NCC MERP in 1995, and its membership includes 22 patient safety groups (NCC MERP, 2005). NCC MERP claims its definition of *medication errors* as a successful development. According to NCC MERP, "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional, patient, or consumer. Such events may be related to professional practice, health-care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use" (NCC MERP, 2005).

This definition has been adopted by the FDA, Centers for Medicare and Medicaid Services (CMS), and USP. The development of a common nomenclature has the potential to enhance the ability of different institutions to share information.

TOOLS FOR IMPROVEMENT

A working group, using the NCC MERP information as a model, could improve the information provided to the prescriber of a drug. The group could bring together experts from academia, practice, pharmacy, and industry, as well as regulators. It could "improve the tools that are already available to communicate the interactions between drugs and their likely consequences," said Dr. Kahn.

The FDA has several related regulatory initiatives to improve drug safety. The electronic labeling rule requires industry to submit e-labels to the FDA beginning in June 2006. This rule requires bar-coding on all over-the-counter medications. MedWatchPlus will unify adverse event

reporting systems and expand communications. The FDA would "like to move into the paperless world," according to Dr. Behrman. Paperless labeling will eliminate the requirement for paper package inserts, which cost companies about $1 million per year per product.

Electronic connectivity will be integral to improving safety, and patient involvement is absolutely necessary. E-prescribing orders drugs in a clear manner and also provides specific information about the patient for whom the medication was prescribed. Access to specific patient information allows a health-care practitioner to appropriately assess potential adverse events based on specific patient knowledge. A problem with databases is that they can only give general information about potential adverse events. Electronic prescribing is enabled in 85 percent of chain drug stores, said Dr. Staffa, but very few of these have the connections necessary to take full advantage of patient-specific information.

In addition to e-prescribing, pharmacists can obtain necessary information about individual cases by simply talking to patients. Pharmacists cannot rely on database information alone. In speaking with a patient, the pharmacist may learn that the doctor is already aware of a particular potential interaction but wants to utilize the combination despite the warnings against it. The pharmacist is also in a unique position to find out what other substances the patient uses that may interact with medications. Information about alcohol, food, and over-the-counter medication is not included in the databases. Dr. Staffa added, "We need to see the pharmacist in a greater service role rather than a product-fulfillment role."

Board certification is a mechanism through which to engage physicians in education concerning the drug safety surveillance system. Cary Sennett, of the American Board of Internal Medicine (ABIM), discussed the ways in which the ABIM uses performance evaluation as part of recertification. The ABIM certifies approximately 180,000 doctors, almost one-third of all practicing physicians in the United States. Certification is not a one-time event; it is a lifelong process that begins with initial certification and requires physicians to maintain their performance through ongoing reevaluations. The certificate holder must pass a secure proctored exam and "demonstrate a commitment to maintain the currency of medical knowledge through ongoing self-assessment of practice performance," added Dr. Sennett. The certificate holder can use practice improvement models (PIMs) to meet this requirement; although current PIMs do not address drug safety explicitly, they include a survey of practice and the infrastructure directly relevant to safe medication management.

"Physicians will continue to participate and will be looking for sources of information to help them meet the maintenance of certification requirement," stated Dr. Sennett. PIMs permit the systematic collection of data relevant to practice performance, such as the way a physician conducts

analysis and plans responses to predictable events. To address the rising demand for better drug safety surveillance, the ABIM is developing a patient safety module that will address drug safety in physician certification and recertification. This project will be completed in late 2006 or early 2007. "Maintenance of certification is a hook through which other quality improvement exercises can be linked or to which they can be attached," said Dr. Sennett.

Assuming that the current level of funding continues, the FDA planned to launch a complete inventory of prescription drugs in the winter of 2006 and an inventory of all marketed drugs by 2008 on the Internet site Facts@FDA/DailyMed. E-prescribing code sets are also planned to be complete and up-to-date by 2008. Further incorporation of drug safety in certification is an important approach to improving education in this area. These new approaches should give the public and health-care providers significantly improved information. Dr. Drazen concluded that in order to improve the system, clear, accurate, and immediately accessible prescribing information should be made available and should be accompanied by expanded data standards, improved passive surveillance, and robust postmarket active surveillance efforts.

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A

Workshop Agenda

Forum on Drug Discovery, Development, and Translation
The Role of Consumers and Health-Care Professionals in Adverse Drug Event Reporting—Key Challenges and Opportunities

November 3–4, 2005
Phoenix Park Hotel
520 North Capitol Street, NW
Washington, DC 20001

Thursday, November 3, 2005

8:30 am **Opening Remarks**

Jeffrey M. Drazen, MD
New England Journal of Medicine

RARE EVENTS AND NEW DRUGS

Topic 1: Recognition and reporting of adverse drug events by physicians including incentives and disincentives (e.g., rhabdomyolysis with statins; Churg-Strauss syndrome with anti-leukotrienes; liver failure with anti-diabetic drugs; opportunistic infections with immune modulators).

8:40 am **Daniel E. Troy, JD**
Sidley Austin Brown & Wood LLP

Anne E. Trontell, MD, MPH
U.S. Food and Drug Administration

Richard Platt, MD, MS
Harvard Medical School

Saira A. Jan, PharmD, MS
Horizon Blue Cross Blue Shield of New Jersey
Rutgers Ernest Mario School of Pharmacy

9:30 am **Discussion**

10:45 am **Break**

Topic 2: Once rare event reports have been received, how to identify possible signal and distinguish it from noise.

11:00 am **Anne E. Trontell, MD, MPH**
U.S. Food and Drug Administration

David Hunt, MD, FACS
CMS Quality Improvement Group

11:20 am **Discussion**

12:15 pm **Lunch**

COMMON EVENTS AND THE MODULATION OF THEIR FREQUENCY BY DRUGS

Topic 1: It is possible that drugs can modify the frequency of occurrence of a relatively common event. How can these events be detected?

1:00 pm **K. Arnold Chan, MD, ScD**
Harvard School of Public Health

Francesca Cunningham, PharmD
U.S. Department of Veterans Affairs

Hershel Jick, MD
Boston University Medical Center

Micky Tripathi, PhD, MPP
Massachusetts eHealth Collaborative

1:50 pm **Discussion**

Topic 2: Once a possible association is detected, how are cause and effect confirmed? Are randomized controlled trials needed or is epidemiology adequate? What is the role of regulators? How does one tease out single drug effects from drug-drug interactions?

2:20 pm **Ronald Krall, MD**
GlaxoSmithKline

Nancy C. Santanello, MD, MS
Merck Research Laboratories

Robert Powell, PharmD
U.S. Food and Drug Administration

Raymond L. Woosley, MD, PhD
The Critical Path Institute

Alastair J. J. Wood, MD
Vanderbilt Medical School

3:10 pm **Discussion**

3:40 pm **Break**

THE ROLE OF PATIENTS AND CONSUMERS IN THE ADVERSE EVENT REPORTING SYSTEM

Topic 1: How should consumers be involved in reporting adverse events? What training and organizational support are needed? How should patient advocacy groups be engaged?

3:55 pm **Marvin M. Lipman, MD, FACP**
Consumers Union

Michael Katz, MBA
International Myeloma Foundation

Karen R. Cox, RN, PhD
University of Missouri Health Care

Alison Rein, MS
National Consumers League

4:40 pm **Discussion**

5:00 pm **Next Steps for the IOM Drug Forum**

5:30 pm **Adjourn**

Friday, November 4, 2005

8:30 am **Opening Remarks**

Jeffrey M. Drazen, MD
New England Journal of Medicine

DRUGS AND ADVERSE HEALTH EVENTS

Topic 1: Is there a comprehensive database of known drug-drug interactions? How is its quality assured? How are the data used? How do we capture events when there are likely multiple sources of drugs?

8:40 am **Jacob Abarca, PharmD, MS**
University of Arizona, College of Pharmacy

J. Russell Teagarden, RPh, MA
Medco Health Solutions, Inc.

Scott Weingarten, MD, MPH
Zynx Health

Sidney Kahn, MD, PhD
Pharmacovigilance and Risk Management, Inc.

9:30 am **Discussion**

Topic 2: Assuming that a database of adverse drug reactions exists (either rare events or common events that occur alone or as a result of drug-drug interactions), should this information be on a uniform drug label that separates adverse drug events and interactions by severity? How do we encourage physicians to use the information?

10:00 am **A. Leander Fontaine, MD**
Pharmiceutics LLC

Rachel E. Behrman, MD, MPH
U.S. Food and Drug Administration

Ed Staffa, RPh
National Association of Chain Drug Stores

Cary Sennett, MD, PhD
American Board of Internal Medicine

10:40 am **Discussion**

11:00 am **Break**

Topic 3: Are there electronic systems that can be used to prompt health care providers to look for adverse drug related events and warn against potential drug-drug interactions? How are these systems deployed?

11:15 am **Peter Kilbridge, MD**
Duke University Health System

Stuart Levine, PharmD
Institute for Safe Medication Practices

11:40 am **Discussion**

12:00 pm **Next Steps for the IOM Drug Forum**

12:30 pm **Adjourn**

B

Speaker Biographies

Jacob Abarca, PharmD, MS, is an Assistant Research Scientist in the Center for Health Outcomes and PharmacoEconomic Research. Dr. Abarca completed his Doctor of Pharmacy and Master of Science degrees at the University of Arizona, College of Pharmacy, graduating summa cum laude. He completed a pharmacy practice residency at the Southern Arizona VA Health Care System. Dr. Abarca's research interests include patient safety, pharmacy practice research, and health technology assessment. He is a member of the Pharmaceutical Outcomes Core for the Arizona Center for Education and Research on Therapeutics (Arizona CERT), which is focused on reducing adverse events caused by drug interactions. He also is a Co-Investigator in an NIH-funded research study investigating the use of telemedicine in rural health-care settings and has served as a consultant for research studies evaluating computerized physician order entry and adverse drug events.

Rachel E. Behrman, MD, MPH, is the Deputy Director, Office of Medical Policy in FDA's Center for Drug Evaluation and Research, and Director of the Task Force on Cross Center Initiatives in the Office of the Commissioner. An internist with a subspecialty in infectious diseases who joined FDA in 1989, Dr. Behrman received her AB in mathematics from Washington University, her MD from Mt. Sinai School of Medicine, and her MPH from The Johns Hopkins School of Hygiene and Public Health.

K. Arnold Chan, MD, ScD, is a Senior Scientist at i3 Drug Safety and an Adjunct Associate Professor at the Harvard School of Public Health. He was the Director of the Harvard Pharmacoepidemiology Program from 2002 through 2005 and was elected a Fellow of the International Society for Pharmacoepidemiology in 2003. Dr. Chan has extensive experience in safety evaluation of pharmaceutical agents and vaccines and has conducted research sponsored by the NIH, FDA, and pharmaceutical companies.

Karen R. Cox, RN, PhD, is the Quality Improvement Coordinator in the Office of Clinical Effectiveness and a Senior Investigator in the Center for Health Care Quality at University of Missouri Health Care in Columbia. She is one of four Missourians who is a graduate of the Patient Safety Improvement Corp, a training partnership with the Agency for Healthcare Research and Quality and the Veteran's Administration. Her areas of practice and research include population-based clinical outcomes improvement; health-care operations redesign; organizational culture change as it relates to patient safety; and faculty, student, and staff curriculum development and instruction in quality improvement, patient safety, and crew training. Beginning in 2000, the Office of Clinical Effectiveness oversaw the design and development of an internal, secure, web-based quality-of-care/patient safety event reporting system. The University of Missouri's adverse event reporting system, implemented on January 1, 2002, is accessible for reporting by staff, physicians, patients, families, and visitors.

Francesca Cunningham, PharmD, is the Director of the Center for Medication Safety PSCI, National Center for Patient Safety (NCPS), and Program Director of Outcomes Research at the Department of Veterans Affairs (VA) Pharmacy Benefits Management/Strategic Healthcare Group (PBM/SHG). Dr. Cunningham was the driving force behind the successful effort of PBM/SHG to establish reliable methods for merging the VA prescription database with other large VA-related databases in order to evaluate the safe and appropriate use of medications in the veteran population. Her focus has been on assessing new agents where safety data is lacking and older drugs when a newly emerging danger requires evaluation. She designed the VAMedSAFE and PBM Drug Safety Quality Improvement (QI) program. Under her direction the program has become a major tool in the evaluation of drug safety in the VA and its role in the formulary decision process. Since her time in the VA, Dr. Cunningham has focused her research efforts in the area of drug safety. Her group has worked independently and with other researchers to perform several drug safety and pharmacoepidemiologic studies. She was awarded a

grant to establish the VA Center for Medication Safety Patient Safety Center of Inquiry by the NCPS.

Jeffrey M. Drazen, MD, is the Editor-in-Chief of the *New England Journal of Medicine*, a post he has held since 2000. During his tenure, the Journal has published major papers advancing the science of medicine, including the first descriptions of Severe Acute Resiratory Syndrome (SARS) and papers modifying the treatment of cancer, heart disease, and lung disease. The Journal, which has over a million readers every week, has the highest impact factor of any journal publishing original research. He attended Tufts University, with a major in physics, and Harvard Medical School and served his medical internship at Peter Bent Brigham Hospital in Boston. Thereafter, he joined the Pulmonary Divisions of the Harvard hospitals. He served as Chief of Pulmonary Medicine at the Beth Israel Hospital, as Chief of the combined Pulmonary Divisions of the Beth Israel and Brigham and Women's Hospitals, and finally as Chief of Pulmonary Medicine at Brigham and Women's Hospital. Through his research, he defined the role of novel endogenous chemical agents in asthma. This led to four new licensed pharmaceuticals for asthma with over 5 million people on treatment worldwide.

A. Leander Fontaine, MD, is President of Pharmiceutics LLC, a Pennsylvania-based company that offers labeling and regulatory consulting, expert services, and training. Before founding Pharmiceutics in March 2005, he was Vice President and Head of Global Labeling Division and Vice President, International Labeling Liaison, Wyeth, USA. He started his career in global labeling in 1991 and has served as head of global labeling functions for Hoechst Marion Roussel (USA) and Hoechst (Germany). He has also held positions in clinical development with Behringwerke (Germany). Before joining the pharmaceutical industry, he worked in internal medicine (German Army Hospital Ulm, Germany) as well as in anesthesiology, intensive care, and emergency medicine (University Hospital Ulm, Germany).

David Hunt, MD, FACS, works in the Quality Improvement Group, a division of the Office of Clinical Standards and Quality (OCSQ) in the Centers for Medicare and Medicaid Services (CMS). At CMS he leverages his clinical expertise in surgery and over 30 years' experience in information systems. He is currently the Government Task Leader for the Medicare Patient Safety Monitoring System (MPSMS) as well as the Surgical Care Improvement Partnership (SCIP), two national projects aimed at advancing the CMS quality improvement and patient safety

agendas. Dr. Hunt, who is licensed to practice medicine in the District of Columbia, is certified by the American Board of Surgery and has been a Fellow of the American College of Surgeons since 1993. Practicing surgery in both private and academic settings, Dr. Hunt served as a Clinical Assistant Professor of Surgery at Howard University, as well as Chair of surgical peer review at various hospitals in the Washington metropolitan area.

Saira A. Jan, PharmD, MS , is the Director of Clinical Programs, Pharmacy Management, at Horizon Blue Cross Blue Shield of New Jersey (BCBSNJ), where she is involved with pharmacy utilization management, formulary management, patient safety initiatives drug information, utilization analysis, research and clinical outcome studies, and disease state management. She is also the Director of the residency program for postgraduate Pharmacy at Horizon BCBSNJ. She is actively involved with research and is the Director of research for Horizon BCBSNJ. Dr. Jan received her Master of Science in Pharmacology from St. John's University in New York and her PharmD from Rutgers, The State University of New Jersey.

Hershel Jick, MD, has since 1966 been Director of the Boston Collaborative Drug Surveillance Program (BCDSP) of Boston University Medical Center, Lexington, Massachusetts and Associate Professor of Medicine, Boston University School of Medicine. He is a graduate of Harvard Medical School. After completing his residency training in internal medicine, he completed a fellowship program in clinical pharmacology and was a Burroughs Wellcome Scholar in Clinical Pharmacology. The BCDSP has pioneered the use of automated databases in drug safety studies. Dr. Jick has together with his colleagues at the BCDSP published more than 300 studies over a 35-year period. In addition, he has organized several international workshops on postmarketing drug studies, the 21st of which was held in France in June 2005, bringing together experts in the field to share information on recent developments in pharmacoepidemiology.

Sidney Kahn, MD, PhD, has been a major contributor to U.S. and international developments in pharmacovigilance, risk assessment, and risk management for many years. After 17 years in academic laboratory medicine in the United Kingdom and United States as a laboratory director and basic researcher, he spent the next 13 years at Bristol-Myers Squibb and Johnson & Johnson working on safety assessment of medicinal products throughout their life cycle. He established Pharmacovigilance & Risk Management, Inc., in July 2002. During his industry tenure, Dr. Kahn participated actively in several U.S. and international pharmacovigilance

working groups. He represented PhRMA in ICH MedDRA Expert Working Goups, including M1 and Points to Consider; he was a member of the CIOMS-VI Working Group, and is currently active in several DIA SIACs including Clinical Safety and Pharmacovigilance, Terminology Management, and Labeling. He is also a participant in the HL7 SPL Implementation Workgroup. Dr. Kahn is a frequent invited presenter at conferences and workshops in the USA and Europe on all aspects of pharmacovigilance and risk management.

Michael Katz, MBA, is a 15-year myeloma survivor. He is Vice President of the International Myeloma Foundation and a member of the Foundation's Executive Board. He is a past Chair of the National Cancer Institute's Director's Consumer Liaison Group and past Chair of the Association of Online Cancer Resources (ACOR). He is Co-Chair of the Eastern Cooperative Oncology Patient Representatives Committee and a member of the Patient Advisory Board of the Coalition of National Cancer Cooperative Groups. Mr. Katz also serves as a patient consultant to the FDA and leads in-person and online multiple myeloma support groups. He has been an active advocate of clinical trials, participating in the design of myeloma trials and working on programs to improve the quality and efficiency of cancer clinical trials at the national level. He is involved in ongoing efforts to improve communications about clinical trials to the advocacy community and to the consumer. Mr. Katz has also been involved in researching post-approval drug safety issues.

Peter Kilbridge, MD, worked at Boston Children's and Massachusetts General Hospital as a pediatrician trained in medical informatics. He then worked as a Practice Director with First Consulting Group, where he founded the company's patient safety practice. Dr. Kilbridge's group worked with The Leapfrog Group to develop a method for testing hospitals' computerized physician order entry systems' ability to prevent medication errors. He has also published studies on safety in medication management, adverse drug event surveillance, the roles and responsibilities of physicians for patient safety, and the cost to hospitals of computerizing physician order entry. At Duke University, Dr. Kilbridge is working with clinicians to track and measure improvements in patient safety and quality. Current projects include the development of an automated system for detection and tracking of adverse drug events across the Duke University Health System; creation of a computerized safety incident reporting system; and measurement and tracking of safety, quality, and operational benefits resulting from the use of computer systems to aid in patient care.

Ronald Krall, MD, is Senior Vice President, Worldwide Development, for GlaxoSmithKline (GSK). His responsibilities include clinical development and regulatory affairs for all GSK compounds in development and products throughout the world. He joined GSK in 2003. Before that, he held positions at AstraZeneca Pharmaceuticals, Abbott Laboratories, and Lorex Pharmaceuticals. He earned a Bachelor's degree in Mathematics from Swarthmore College and his MD from the University of Pittsburgh, trained as a Staff Associate at the National Institutes of Health Epilepsy Branch, and completed his training in neurology and clinical pharmacology at the University of Rochester. He is board certified in neurology and is Immediate Past President of the National Sleep Foundation, a member of the Board of Directors of the Delaware Valley Science Fairs, and a past Trustee of the American Academy of Pharmaceutical Physicians.

Stuart Levine, PharmD, is the Informatics Specialist at the Institute for Safe Medication Practices (ISMP). His primary role is promoting medication safety through the safe use of technology. He also serves as an in-house resource for medication safety for pediatric and neonatal patients based on his 25 years' experience as the Director of Pharmacy Services at the Alfred I. duPont Hospital for Children in Wilmington, Delaware. He is a member of the consulting team at ISMP and assists in reviewing the medication use process in hospitals around the country. He has served as both member and officer of local pharmacy organizations as well as a member and president of the Delaware State Board of Pharmacy. Nationally Dr. Levine is a member of the board of the Pediatric Pharmacy Advocacy Group (PPAG) and is currently PPAG's chief operating officer. He received his Bachelor of Pharmacy degree from Temple University and his Doctor of Pharmacy degree from the University of Kentucky.

Marvin M. Lipman, MD, FACP, has been Consumers Union's Chief Medical Adviser since 1967, has been Medical Editor of *Consumer Reports,* and has been Medical Editor of *Consumer Reports on Health* since its inception in 1989. He has represented Consumers Union on advisory panels of the Food and Drug Administration and the United States Pharmacopeia (USP). He was a member of the 2000–2005 board of trustees of the USP and represented the public. A graduate of Columbia University's College of Physicians and Surgeons, Dr. Lipman is a practicing physician, board certified in internal medicine and endocrinology. He is a Fellow of the American College of Physicians and the American College of Endocrinology and is Clinical Professor of Medicine (emeritus) at New York Medical College in Valhalla.

Richard Platt, MD, MS (Epidemiology), is Professor and Chair of the Department of Ambulatory Care and Prevention at Harvard Medical School and Harvard Pilgrim Health Care, a New England HMO that supports research and teaching. He is also Professor of Medicine at Harvard Medical School and the Brigham and Women's Hospital, where he is Hospital Epidemiologist. He is a member of the Food and Drug Administration Drug Safety and Risk Management advisory committee, the American Association of Medical Colleges' Advisory Panel on Research, and the national steering committee for Agency for Healthcare Research and Quality Centers for Education and Research in Therapeutics (CERTs). He is the former Chair of the National Institutes of Health study section Epidemiology and Disease Control 2, former Chair of the Centers for Disease Control and Prevention Office of Health Care Partnerships' steering committee, former Co-Chair of the Board of Scientific Counselors of the CDC's Center for Infectious Diseases, and former chair of the executive committee of the HMO Research Network. His research focuses on improving population health through health plans' providers and data and through health plans' ability to communicate with their members. Examples include the use of automated record linkage systems to improve the safety and assess the effectiveness of prescription drugs and to detect and control both hospital- and community-acquired infections.

Robert Powell, PharmD, is Director, Pharmacometrics, Office of Clinical Pharmacology & Biopharmaceutics, Food and Drug Administration. Previously, he was the Senior Vice President, Drug Development Consulting Services, Pharsight Corp., where he worked with internal consultants and industry partners to increase drug development productivity through modeling and simulation of clinical trials and application of software products. Dr. Powell's previous positions include Vice President, Pharmacokinetics, Dynamics and Metabolism, at Parke Davis (1996–2001) and Pfizer and Director of Clinical Pharmacology at GlaxoSmithKline (1987–1996). These departments have excelled in the application of pharmacokinetic/dynamic principles from discovery through regulatory approval in better defining dose-response and contributing to development decisions. Dr. Powell has led various committees on drug development project governance and drug development efficiency. He received his pharmacy training at West Virginia University and his clinical pharmacy training at Philadelphia College of Pharmacy and Science, and did a National Institutes of Health postdoctoral fellowship in pharmacokinetics at the University of California at San Franciso. He spent 10 years in academics (Arizona, North Carolina) in clinical pharmacokinetics and clinical pharmacology. He has published over 100 peer-reviewed articles and book chapters.

Alison Rein, MS, is the Assistant Director of Food & Health Policy at the National Consumers League (NCL). Founded in 1899 to bring consumer power to bear on marketplace and workplace issues, NCL is the nation's oldest consumer organization. Ms. Rein designs and coordinates campaigns and other activities around NCL's priority issues, including food safety and nutrition, medication safety, and health care quality. In the last year, she has expanded NCL's involvement as a consumer stakeholder in the national discussion about emerging health technologies. Prior to joining NCL, Ms. Rein served as a health care consultant to a number of private and non-profit organizations, for which she conducted strategic evaluations, market studies, and research efforts aimed at evaluating the cost-effectiveness of numerous drug, biologic, and device interventions. She holds a Master's degree in public policy analysis from the University of Rochester and has coauthored several articles published in peer-reviewed medical journals.

Nancy C. Santanello, MD, MS, is a physician-epidemiologist trained in Emergency Medicine and Preventive Medicine with a Master of Science degree in Epidemiology. She is board certified by the American College of Preventive Medicine in Preventive Medicine and Epidemiology. Dr. Santanello received her undergraduate degree in 1971 from Marymount College of Fordham University and her medical degree in 1982 from Howard University School of Medicine. She was a Medical Officer with the National Heart, Lung, and Blood Institute (NHLBI) Prevention and Demonstration Research Branch of the Division of Epidemiology and Clinical Applications (1987–1991). From 1991 to present, she has been in the Department of Epidemiology at Merck Research Laboratories; in 2003 she was appointed to the Head of that department. Her areas of research interest include the development and validation of outcome measures for use in clinical trials; study design; adherence to therapy; satisfaction with and preference for therapy; effectiveness studies; pharmacoepidemiology; and interventions related to chronic diseases, particularly respiratory, migraine, and cardiovascular diseases. Dr. Santanello has published over 45 peer-reviewed manuscripts. She has been invited to speak on outcome measurement issues at several national and international meetings. In 1998 she received the Merck Directors Award, the Company's highest honor, from the Board of Directors for her work in support of outcomes research measures for asthma.

Cary Sennett, MD, PhD, is Senior Vice President for Research and Development at the American Board of Internal Medicine. Prior to that, he led research and development at Ingenix, a UnitedHealth Group company that provides health intelligence to firms in all sectors of health care. Before

joining Ingenix, Dr. Sennett was Vice President for Science and Quality Improvement at the American College of Cardiology (ACC), Executive Vice President for Health Information Services at BenefitNation, a provider of Internet applications in the health-care industry, and Executive Vice President at the National Committee for Quality Assurance (NCQA). He also spent five years as a quality leader at Aetna, at US Healthcare, and at Group Health Cooperative of Puget Sound. Dr. Sennett received his MD from Yale University and did his residency training at Harvard's Brigham and Women's Hospital. After his clinical training, he completed a Kaiser Foundation Fellowship in Health Policy and Management at the Massachusetts Institute of Technology, from which he received his PhD. Dr. Sennett is a frequent speaker and author on issues of quality improvement in health care. He has been a member of the editorial boards of the *Joint Commission Journal on Quality Improvement, Quality Management in Health Care*, and the *American Journal of Managed Care* and served as founding Editor-in-Chief of *Preventive Medicine in Managed Care*. He was Co-Chair of the Steering Committee on Hospital Measurement for the National Quality Forum (NQF) and currently serves as the Chair of NQF's Technical Advisory Panel on Cardiovascular Ambulatory Care measures.

Ed Staffa, RPh, is the Vice President of Pharmacy Practice and Communications with the National Association of Chain Drug Stores (NACDS). An eight-year veteran of NACDS, Dr. Staffa is involved with the writing and editing of a variety of publications with NACDS, including a weekly communication to CEOs and executive-level chain pharmacy operators and a monthly newsletter for practicing pharmacists. His responsibilities extend to all issues affecting the practice of pharmacy, such as those relating to patient safety, billing for non-dispensing pharmacy services, and medication therapy management services. He is also involved with the chain drug store industry's efforts to educate the general public about the role of the community pharmacist in health care and improve medication use among patients. Dr. Staffa is a 1981 graduate of the University of Rhode Island School of Pharmacy. Prior to coming to NACDS in 1997, Dr. Staffa served as a practicing pharmacist in a variety of community settings in the Washington, DC, area for 16 years.

J. Russell Teagarden, RPh, MA, currently serves as Vice President of Clinical Practices & Therapeutics at Medco Health Solutions, Inc. He joined Medco in July 1993 as Director of Clinical Programs. Prior to joining Medco, he served for 12 years as a Drug Information Specialist and as a clinical pharmacist specializing in critical care in the Chicago teaching hospital community. During this time, Mr. Teagarden held an academic

appointment at the University of Illinois College of Pharmacy as Assistant Professor of Clinical Pharmacy. He serves as a member of the Board of Trustees of the Institute for Safe Medication Practices and as a member of the Board of Trustees of the Pharmacy & Therapeutics Society. He also serves on the Oversight Body of the American Medical Association Ethical Force Program. Mr. Teagarden received a Bachelor of Science degree in Pharmacy from the University of Illinois College of Pharmacy, and he completed a residency in hospital pharmacy at Northwestern University Medical Center in Chicago. He also holds a Master of Arts degree in Research Methodology from Loyola University of Chicago and is currently a candidate for a Doctorate in Medical Humanities at the Caspersen School of Graduate Studies of Drew University. He has published several papers on significant medical, pharmacy, and ethics issues.

Micky Tripathi, PhD, MPP, is the President and Chief Executive Officer of the Massachusetts eHealth Collaborative (MAeHC), a non-profit collaboration of 34 leading Massachusetts organizations. He is also a member of the Board of Directors of MA-SHARE, a community utility service for statewide clinical data exchange in Massachusetts. Prior to joining MAeHC, Dr. Tripathi was a manager in the Boston office of the Boston Consulting Group (BCG), a leading strategy and management consulting firm. While at BCG, he served as the founding President and CEO of the Indiana Health Information Exchange, an Indianapolis-based non-profit company partnered with the Regenstrief Institute to create a statewide health information infrastructure in the state of Indiana. As a manager in BCG's health care practice, Dr. Tripathi also served a variety of U.S. and international clients in the non-profit sector as well as in the bioinformatics, biotechnology, and pharmaceutical industries. He holds a PhD in political science from the Massachusetts Institute of Technology, a Master of Public Policy from Harvard University, and an AB in political science from Vassar College. Prior to receiving his PhD, he was a Senior Operations Research Analyst in the Office of the Secretary of Defense in Washington, DC, for which he received the Secretary of Defense Distinguished Civilian Service Award.

Anne E. Trontell, MD, MPH, is the Deputy Director of the Office of Drug Safety (ODS) in the FDA Center for Drug Evaluation and Research. Since coming to FDA in 1996, she has served as the Director of the Division of Surveillance, Research, and Communication Support in ODS, the Deputy Director and Acting Deputy Director of the Divisions of Drug Risk Evaluation I and II, and a medical reviewer in the Division of Pulmonary and Allergy Drug Products. Prior to 1996, Dr. Trontell was Chief Scientist in the Office of Research and Demonstrations at the Health Care Financing

Administration (HCFA), where she conducted and supervised outcomes research on preventive services use by Medicare beneficiaries. While at HCFA, she managed a national public health outreach campaign to promote use of the Medicare mammography benefit. Her experience in epidemiology includes work with the Centers for Disease Control and Prevention, where she served as an Epidemic Intelligence Service Officer at the National Center for Health Statistics and the Office on Smoking and Health. Prior to obtaining her advanced degrees, she did contract research in environmental health and toxicology for the Environmental Protection Agency and other federal agencies. Dr. Trontell trained in pediatrics at The Children's Hospital in Boston, in medicine at the University of Pennsylvania, and in public health at the Harvard School of Public Health.

Daniel E. Troy, JD, a partner in Sidley Austin Brown & Wood LLP's Life Sciences Practice as well its Appellate Litigation group, is the former chief counsel of the Food and Drug Administration (FDA). In addition to providing strategic counseling on FDA-related matters, Mr. Troy practices administrative and constitutional law and litigation, with particular focus on the pharmaceutical, biotechnology, food, medical device, cosmetic, and media industries. Mr. Troy, who will head the ABA's Section of Administrative Law and Regulatory Practice beginning in September 2006, was the first appointee to the FDA made by President George W. Bush. In that capacity, he reviewed and approved major regulations and important guidances issued during that time. He played a key role in the drafting of the rule modifying the process by which generic drugs come to market and successfully argued two Hatch-Waxman cases for the FDA. Mr. Troy has testified before the Senate and House Judiciary Committees and the House Committee on Science, as well as before many state and local bodies. He has given more than 140 speeches on topics that include Hatch-Waxman reform, preemption, a variety of First Amendment and other constitutional issues, telecommunications, the role of the courts, and administrative law.

Scott Weingarten, MD, MPH, is the President, Chief Executive Officer, and Co-Founder of Zynx Health. Additionally, he is a Clinical Professor of Medicine (Step II) at the UCLA School of Medicine and the Director of Health Services Research at Cedars-Sinai Health System. Dr. Weingarten was also a tenured Professor of Medicine (in residence) at the UCLA School of Medicine. After graduating from the UCLA School of Medicine, he completed his internship, residency, and fellowship in internal medicine at Cedars-Sinai Medical Center. He later participated in a National Center for Health Services Research Fellowship at the RAND/UCLA Center for

Health Policy Study. During the fellowship, he earned a Master of Public Health degree at the UCLA School of Public Health. Dr. Weingarten has also worked as a primary care physician at Kaiser Permanente. He is a Fellow of the American College of Physicians. He has published more than 100 articles, editorials, and book chapters on quality improvement and related topics and serves on the editorial boards of five publications. He was a member of the Disease Management Advisory Committee of NCQA and has represented the American College of Physicians on health care issues in Washington, DC, and Sacramento. Dr. Weingarten won the President's Award and the Golden Apple Teaching Award at Cedars-Sinai Medical Center, as well as the Society of General Internal Medicine Award for Outstanding Educational Workshop. He has given more than 250 presentations on evidence-based medicine, computerized physician order entry, quality improvement, disease management, outcomes measurement, and related subjects throughout the United States and internationally. Dr. Weingarten was a Quality Leader for the American College of Physician Executives and was on the Executive Committee of the Board of Directors of the Institute for Medical Quality. He currently serves on the Steering Committee for the American Heart Association "Get With The Guidelines," the Healthcare Information and Management Systems Society Patient Safety and Quality of Care Committee, and the Quality Improvement Committee of the Board of Directors of St. Joseph's Health System (14 acute care hospitals).

Alastair J. J. Wood, MD, is a tenured Professor of both Medicine and Pharmacology and an attending physician at Vanderbilt Medical School, where he is also Associate Dean. Dr. Wood is a member of many societies and has received numerous honors, including election to membership of the American Association of Physicians (AAP) and the American Society for Clinical Investigation (ASCI); Honorary Fellow, American Gynecological and Obstetrical Society (AGOS); Fellowship of the American College of Physicians; Fellowship of the Royal College of Physicians of London; and Fellowship of the Royal College of Physicians of Edinburgh. He was the 2005 recipient of the Rawls-Palmer Award in recognition of "drug investigation that brings the effects of modern drug research to the care of patients" from the American Society for Pharmacology and Therapeutics. Dr. Wood serves on a number of editorial boards, most notably that of the *New England Journal of Medicine*; he was the Drug Therapy Editor of the *New England Journal of Medicine* from 1985 to 2004. He is also on the editorial board of *Clinical Pharmacology and Therapeutics*. He has previously served on the editorial board of the *British Journal of Clinical Pharmacology*. Dr. Wood is currently the Chairman of the FDA's Nonprescription Drugs Advisory Committee and recently chaired the

FDA Advisory Committee on COX-2 drugs. His research interests have been focused on understanding the mechanisms for inter-individual variability in drug response, with a particular focus on the molecular genetics of adrenergic receptors, ethnic differences in drug response, vascular response, and the genetics of drug metabolism. His research has been continuously funded by NIH and has resulted in over 250 articles, reviews, and editorials.

Raymond L. Woosley, MD, PhD, earned a PhD in Pharmacology from the University of Louisville and an MD from the University of Miami. Dr. Woosley specialized in Internal Medicine and Clinical Pharmacology at Vanderbilt University, where he rose to the rank of Professor of Medicine. At Georgetown University he served as Chairman of the Department of Pharmacology and in 2000 was appointed Associate Dean for Clinical Research. In 2001 he became Vice President for Health Sciences at the University of Arizona and Dean of the College of Medicine. In January 2005 he assumed the position of President of The Critical Path Institute (C-Path), a non-profit corporation formed by the Food and Drug Administration, SRI International, and the University of Arizona to accelerate the development of safe innovative medicines. Since 1999, he has directed one of seven federally funded Centers for Education and Research on Therapeutics (CERT). Dr. Woosley's research has been published in over 260 publications and has investigated the basic and clinical pharmacology of drugs for the drug treatment of arrhythmias and the cardiac toxicity of drugs. His research discovered the mechanism of the toxicity of the antihistamine Seldane, which contributed to its subsequent removal from the market. For his contributions to medicine, he received the Rawls-Palmer Award from the American Society of Clinical Pharmacology and Therapeutics and the FDA Commissioner's Special Citation for his work to advise the agency on the toxicity of dietary supplements containing ephedra. In addition, Dr. Woosley is a Past President of the Association for Medical School Pharmacology and the American Society for Clinical Pharmacology and Therapeutics. His current research is on the prevention of adverse drug interactions.