The way in which important, emerging information about the safety of marketed drugs is communicated to the public and health-care professionals has changed remarkably over the past 5 years. In an environment of instant and global electronic communication, and in response to the challenge of meeting the public’s expectations of transparency and accountability, the US Food and Drug Administration (FDA) has implemented new communication tools, including early communications about ongoing safety reviews, and new policies that describe what and when we communicate. In 2009, the FDA will complete a major overhaul of its website, one of its principal vehicles for communication.

**EVOlUTION OF DRUG-RISK COMMUNICATION**

In the 1500s, an ethical statute of the Royal College of Physicians stated, “Let no physician teach the people about medicines or even tell them the names of the medicines, particularly the more potent ones … for the people may be harmed by their improper use.” Those who violated this principle were fined 40 shillings. Four centuries later, in 1938, the US Food and Drug Administration (FDA) said that drug labels “should be written ‘only in such medical terms as are not likely to be understood by the ordinary individual.’” For centuries, the physician has served as the “learned intermediary,” deciding which medications are appropriate for a patient’s treatment and determining what information the patient should have about the treatment.

In modern clinical practice, health-care providers can no longer limit their communications to orders for treatments and testing and to directions for use of a medication. Today, both patient expectations and standards of care require engagement of patients and their caregivers at all levels of medical decision making and health-care delivery.

Since the FDA’s establishment in 1906, the professional label (the “drug label”)—produced and distributed by the drug manufacturer, reviewed and approved by the FDA, and written for the health-care professional—has served as the primary source of information about a drug. Clinicians and pharmacists alike continue to shoulder the responsibility of proper prescribing and instructing patients in the safe and appropriate use of a medicine. The drug label has recently been modified to make it more useful and accessible to the consumer. In January 2006, the FDA changed the format, adding a “Highlights” section to summarize key prescribing information, including points that physicians should discuss with their patients. (The new requirements can be found at http://www.fda.gov/cder/regulatory/physLABEL/physLabel_qa.htm.)

In response to changing societal expectations, the role of the FDA has evolved from providing information aimed solely at the health-care provider to communicating health-related information directly to patients and the general public. The professional label is now supplemented by information intended for the consumer. Since the 1990s, two forms of regulated consumer information—the medication guide and the patient package insert—have been available for selected drugs. The medication guide, a pharmacy handout that comes with many prescription medicines, is deemed necessary when the FDA determines that information directed to the patient could prevent serious adverse events or affect a patient’s decision to use, or continue to use, a product, or when adherence to directions is crucial to a drug’s effectiveness (21 CFR §208). The Food and Drug Administration Amendments Act of 2007 designated medication guides an important component of a Risk Evaluation and Mitigation Strategy (Lists of medication guides and the Risk Evaluation and Mitigation Strategy that requires them can be found at http://www.fda.gov/cder/drugSafety.htm).

A patient package insert, which is required to be distributed with certain drugs (e.g., oral contraceptives and estrogen-containing products), is included in the manufacturer’s packaging. It is designed to inform the patient about the nature of the drug, its proper use, and warnings and side effects.

In the past decade, attention to postmarket safety issues has increased markedly. Close to half a million adverse event reports are submitted to the FDA annually for marketed products. New information from ongoing clinical trials, observational studies,
and meta-analyses of trial and epidemiologic data is submitted to the FDA regularly, and new studies of drug risks appear in the scientific literature almost weekly. This information forms the basis of the agency’s ongoing risk evaluation of marketed products. In addition, high-profile safety issues, such as the sudden withdrawal of rofecoxib from the market in September 2004 over cardiac safety concerns and the widespread media attention to the use of antidepressants in children and the risk of suicidality, have focused attention on postmarket safety concerns. These events led to calls from many quarters of society for the FDA to be more open and transparent about the safety issues it is evaluating, and to be timelier in providing information about issues under consideration—sometimes before the agency has reached a conclusion about the significance of its review or about actions to be taken as a result.

In February 2005, the Secretary of the Department of Health and Human Services, Michael Levitt, announced a drug safety initiative that included a call for the agency to become more open and transparent: “We will keep the promise of the FDA brand by putting in place more rigorous oversight and collecting and sharing important and emerging information about drug safety and effectiveness.” In response, the FDA’s Center for Drug Evaluation and Research introduced new communication tools. A draft guidance published in May 2005 and finalized in March 2007, Drug Safety Information—FDA’s Communication to the Public, alerted the public to the basis for and purpose of these communications (http://www.fda.gov/cder/guidance/7477fnl.htm).

COMMUNICATING DRUG SAFETY INFORMATION IN 2008

In all its communications, the FDA strives to explain the issue clearly, to outline any actions that professionals and the public should take, and to summarize the scientific basis for its recommendations in a manner suited to the intended audience. Effective, balanced communications should foster an understanding of the reason for approval of a drug, the benefits of the drug, and the potential risks that accompany its use. The science surrounding drug approvals and the postmarket assessment of emerging risks is complex and often uncertain. Good communication is critical to ensuring that products continue to be used both appropriately and with care.

WHY COMMUNICATE RISK?

Changing societal expectations of and attitudes toward government agencies and health-care providers about the need for greater transparency must be viewed in the context of the extraordinary advances in medical care and public health of the past century. Many once-common potentially lethal diseases have been largely eliminated from industrialized nations, leading the public to take for granted the benefits of medical interventions, including medications, and to perceive many of these interventions as risk free.1 FDA focus-group testing indicates that many people assume that if a drug is approved, then it is safe, and that “safe” means no chance of a serious reaction. Because all medications have associated risks, it is more important than ever for the FDA to clearly articulate and communicate issues regarding drug safety to the public and to reinforce the message that with the benefits of medicines comes some degree of inherent risk.

Timely and appropriate risk communication promotes trust through transparency and facilitates good decision making, either by the public or in the examination room.2,3 Table 1 lists some of the reasons for communicating risk and the expected benefits and potential consequences of such communication. As with taking a medicine, in which the goal is to maximize the benefits while minimizing the risks, so it is with communicating information, in which the desired outcome is appropriate use of a medicine with the fewest unanticipated consequences.

THE MESSAGE AND THE AUDIENCE

The FDA has developed a variety of tools to communicate to professional and general audiences the agency’s current assessment of the relationship between a drug and an adverse event. Ferner and Aronson4 note three categories of potential harm relating to a drug that make communication difficult: lack of proof of the causality of an association, theory or unvalidated anecdotes, and poor estimates of the probability of harm and its likely seriousness and intensity.

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**Table 1** Pros and cons of communicating drug risk information

<table>
<thead>
<tr>
<th>Reason</th>
<th>Expected benefits</th>
<th>Potential consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>The public wants to know about drug safety and drug risks</td>
<td>Transparency fosters greater trust</td>
<td>Risk information, if provided without context, could deter some consumers from taking necessary medicines</td>
</tr>
<tr>
<td>Complete information allows for a more informed and better choice</td>
<td>More information leads to better and more appropriate prescribing and use decisions</td>
<td>Some consumers do not want to be involved or engaged in decision making, preferring to have choices made for them</td>
</tr>
<tr>
<td>Adverse events might be avoided if health-care providers and patients know what adverse events to be aware of and what steps can be taken to mitigate any serious outcomes</td>
<td>Such knowledge could lead to fewer or less serious adverse events</td>
<td>Some adverse events are unavoidable despite best care; communication may lead to unrealistic expectations that all adverse effects can be avoided or prevented</td>
</tr>
<tr>
<td>Communicating drug risk information supports patient autonomy in decision making</td>
<td>This is consistent with trends toward patient input into health-care decision making</td>
<td>Patients might give excessive weight to small risks when considering the benefits of a therapy</td>
</tr>
<tr>
<td>Failure to communicate drug-risk information may undermine confidence in drugs and lead to underuse of effective therapies (Campbell and Califf)</td>
<td>Communicating drug risk information can foster trust in the development, regulation, and prescription of medicines</td>
<td>Not communicating drug risk information could lead to patients pursuing untested or unregulated therapies and thus lead to more adverse events</td>
</tr>
</tbody>
</table>
When the data linking the use of a drug with an adverse event are clear, the communication reflects the FDA's greater certainty about causality. In this situation, the FDA communication provides the data, the interpretation, the mitigating factors, and the steps that health-care providers and patients can take to reduce the risks.

When the relationship between the use of a drug and an adverse event is clear, the FDA communicates using an Information for Healthcare Professionals (HCP) sheet or a Public Health Advisory (PHA). An HCP sheet outlines the safety issue, states how clinicians and patients can mitigate risk, and provides a summary of the relevant data. An HCP sheet is also used to discuss a safety-related regulatory action, such as a labeling change. A PHA is used to communicate important drug safety information to health-care professionals and the general public, including users or potential users of a drug. A PHA is written in nontechnical language and outlines an issue's seriousness and any steps that might reduce risk. Both HCP sheets and PHAs generally discuss a safety issue about which the FDA has drawn a conclusion.

In contrast, when data are emerging and the review of an issue is ongoing, the FDA uses a recently introduced tool, the Early Communication About an Ongoing Safety Review.

FDA communications can be based on drug-risk information from many sources, including postmarket surveillance, clinical studies, epidemiological studies, the scientific literature, and citizen petitions. Regardless of the source, it is the intended audience and the state of the FDA's assessment that determine the choice of the communication tool or tools.

EARLY COMMUNICATION ABOUT AN ONGOING SAFETY REVIEW

The early communication format was developed by the FDA to keep practitioners and the public informed of important postmarket safety issues under evaluation and to supplement other tools for communicating safety issues to the public. It communicates safety information before conclusions have been drawn and usually before regulatory action has been taken. Because new information about most marketed drugs is constantly being received and reviewed, factors considered in deciding when to issue an early communication are whether the safety issue could affect prescription or use of the drug, whether specific actions can be taken by health-care professionals or patients to prevent harm, whether unapproved use poses a chance for harm, and whether the safety issue affects a vulnerable population.

An early communication is typically brief, limited in scope, and time sensitive. It outlines the potential safety issue, the data to be reviewed, and an expected time frame for the review. It can relate to a single drug or class of drugs.

Figure 1 reproduces the early communication regarding omeprazole and esomeprazole, which discussed a possible association between these drugs and cardiovascular risk (see Appendix for the link to the document online).

After the final review, an update is issued that presents the FDA's conclusions. Updates also indicate whether the drug label was changed or another mechanism was used to convey drug-risk information to health-care professionals and the public. In the case of omeprazole and esomeprazole, the FDA concluded that long-term use of these drugs was unlikely to be related to heart problems and that health-care providers should continue to prescribe, and patients continue to use, these drugs in accordance with the product labeling. This update was released in December 2007, four months after the initial early communication.

EARLY COMMUNICATIONS, 1 JANUARY 2007 TO 30 NOVEMBER 2008

As of 30 November 2008, 16 early communications had been issued (Table 2). Updates have been issued for 8 of these early communications; the remaining 8 are still under review. When appropriate, early communications are updated when additional data are received or analyses are completed by the FDA. The Appendix provides the web link for each of the 16 early communications and any updates. All PHAs, HCP sheets, and early communications are available to the public at http://www.fda.gov. They are distributed electronically to the more than 120,000 members of the MedWatch LISTSERV and to the more than 140 MedWatch health-care organization partners.

CHALLENGES AND THE FUTURE OF RISK COMMUNICATION

To communicate risk information about drugs effectively, the FDA must select an appropriate format and tailor the content so that the intended audience can use the information to make decisions about using a medicine. In crafting messages,
the FDA is sensitive to how basic thought processes in decision making influence risk perception, as described by Fischhoff and Downs.5

- People simplify
- Once people’s minds are made up, it is hard to change them
- People remember what they see
- People cannot detect omissions from the evidence they receive
- People may disagree more about what “risk” is than about how large it is

Fischhoff and Downs5 also note that people understand risks better when their attention is drawn to the information and it is presented in a manner that is easy to comprehend. To make an appropriate impact, the FDA seeks to communicate simply and comprehensibly on topics that are relevant and important. The timing of a risk communication is an important factor in determining whether the desired effect of informing, persuading, or changing behavior is achieved. A safety message received in close proximity to a decision about prescribing or use is more likely to be noticed and acted on.

When safety concerns that relate to a class of drugs are described, it is challenging to convey differential risks among the drugs within that class. Avorn6 cites examples of this challenge: concerns about suicidality with the use of anti-depressants and cardiovascular risk with the use of nonsteroidal anti-inflammatory drugs. He envisions a communication process driven by better quantification of both good and bad outcomes. He captures the challenge for the FDA by noting that when a level of risk has been estimated for use of a drug, the FDA and the industry “must then describe it to prescribers and patients in a way that will inform rather than disorient.”

Mazor et al.7 describe challenges in communicating to healthcare professionals via a “Dear Doctor” letter. These include persuading the reader to trust the source of the information, getting the attention of the reader, providing information in a format that is reader-friendly, and presenting balanced, timely, and succinct information.

The FDA must take full advantage of the science of risk communication. It must rigorously evaluate the impact of its messages on professionals, patients, and caregivers. The recently established Risk Communication Advisory Committee is charged with providing advice to the FDA on best practices in communicating safety issues to the public based on scientific research into risk communication. In 2008, the committee made several recommendations to enhance the FDA’s risk-communication activities. These recommendations include treating risk communication as a core activity, planning and providing resources to support it, and using outside expertise to obtain research findings so that FDA risk communications are grounded in evidence. The committee also advised the FDA to develop partnerships with patient and health-care professional organizations and associations (http://www.fda.gov/oc/advisory/OCRCACACpg.html). Recognizing the importance of its website as a communication tool and source of information, the FDA has launched a major redesign to make information about the products it regulates more accessible (http://www.fda.gov). The new website, to be launched in early 2009, will have special pages for consumers and health-care professionals, will be more user-friendly in its organization, and will make information more easily searchable.

Transparency, accountability, and the provision of timely, useful information come with many potential risks and rewards and numerous opportunities to improve our ability to communicate. The FDA recognizes that communications must be based on the best evidence if they are to be successful and that partnerships with health-care institutions, professional associations, consumer groups, academia, and the pharmaceutical industry are required to ensure that timely, balanced information about the safe and effective use of medicines is made available to everyone.

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CONFLICT OF INTEREST
The authors declared no conflict of interest.

**APPENDIX**

**Links to Early Communications and Updates**
(The name of the drug or drug class is included in the URL.)

http://www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole.htm
http://www.fda.gov/cder/drug/early_comm/bisphosphonates.htm
http://www.fda.gov/cder/drug/early_comm/aprotinin.htm
http://www.fda.gov/cder/drug/early_comm/cefepime.htm
http://www.fda.gov/cder/drug/early_comm/varenicline.htm
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http://www.fda.gov/cder/drug/early_comm/mycophenolate.htm
http://www.fda.gov/cder/drug/early_comm/TNF_blockers.htm
http://www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin.htm
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