Washington REPORT

Risk Management Shapes FDA Policies and Practices

Jill Wechsler

FDA is establishing new offices and launching new initiatives to prompt manufacturers to assess and address drug safety issues.

Ensuring that new drugs are used safely and appropriately after they reach the market is a growing concern among FDA officials. Several highly publicized drug recalls in recent years have heightened public alarm about possible exposure to unsafe and risky medical products. Reports from the Institute of Medicine have revealed the deadly effects of thousands of medication errors associated with the unsafe use of approved therapies. Patient advocates charge that the speedier FDA drug approval process made possible by manufacturers' user fees prevents the agency from detecting and assessing potentially important safety problems.

FDA has implemented several administrative and policy changes in recent months to more effectively respond to safety questions concerning the use of medical products. CDER has established its new super office, the Office of Pharmacoepidemiology and Statistical Science (OPSS), to oversee drug and safety responsibilities. This operation will be expanded by additional funding provided for CDER postmarketing surveillance and risk assessment activities under the recently reauthorized user fee program (see *Pharmaceutical Technology*'s "Washington Report," July 2002). FDA also has convened an advisory panel to offer expert views about safety and risk concerns involving specific drugs as well as about FDA policy regarding these issues.

Public hearings and conferences have provided venues for discussion about the need for new approaches to drug safety and risk management. The search for effective risk management as well as for additional federal funding has been articulated by FDA deputy commissioner Lester Crawford, who previously was involved with the safety assessment of food and veterinary medicines. In his testimony before Congress regarding FDA's 2003 budget proposal, Crawford emphasized the importance of identifying risks associated with the use of medical products to reduce adverse events as well as the need for additional funding to enhance adverse-event data systems. As many as half of patient deaths and injuries associated with the use of FDA-regulated products could be avoided by fully implementing education and information initiatives, Crawford stated.

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Balancing risks and benefits

FDA officials must weigh concerns about drug safety against evidence of potential benefit provided by many new medical products. Despite reported safety problems associated with some pharmaceuticals, the regulators realize that many risky treatments offer important therapeutic value to certain patient populations.

No drug is one hundred percent safe, emphasizes CDER director Janet Woodcock. She points out that accelerating drug development and market approval gives Americans early access to many new therapies but also reduces the amount of information available to the medical community about possible adverse side effects from a newly approved drug. Woodcock and her colleagues are working with pharmaceutical manufacturers to develop risk management programs that can minimize the effects of known risks as well as improve detection and assessment of risks that are unknown when a new drug comes to market.

These efforts promise to have a noticeable influence on drug development, testing, and manufacturing. Traditional ways to prevent unsafe uses of medicines (e.g., labeling revisions and educational programs for prescribers and patients) now appear inadequate for reducing medication errors and avoiding unsafe practices. Consequently FDA officials, in a quest for additional risk management tools, are asking manufacturers to address risk factors earlier in the drug development process and extend postapproval surveillance and risk management efforts.

Reorganization addresses risk

FDA's growing interest in risk management is apparent in several management initiatives at the agency. Last year Woodcock recruited government epidemiological experts to oversee the agency's new risk management activities. Steven Galson came from the Environmental Protection Agency to be CDER deputy director and supervise the agency's expanded involvement in postmarketing risk management. A few months later, Galson's colleague Paul Seligman moved from the Department of Energy to head what is now OPSS (see sidebar "Who's who in FDA risk management").

OPSS includes the Office of Drug Safety (ODS, formerly the Office of Postmarketing Drug Risk Assessment), which looks for signals of safety concerns from adverse-event reports and postapproval research by manufacturers. The Office of Biostatistics also was shifted to OPSS and continues to provide statistical analysis of clinical trial and postmarketing data to evaluate safety and efficacy reports (see sidebar "OPSS oversees pre- and postmarket safety issues" and Figure 1).

Public focus

FDA officials have been discussing postmarketing safety concerns at conferences and public meetings. In May, FDA held a public hearing about risk management to solicit concerns and proposals from manufacturers, healthcare organizations, pharmacists, and patients about ways to improve risk communication and to develop methods for better managing risky pharmaceuticals. The Drug Information Association–sponsored workshop "Risk Management Comes of Age" held in Bethesda, Maryland, in May examined the effects of FDA initiatives on the drug approval process and postapproval safety programs.

At the annual meeting of the International Society for Pharmacoeconomics and Outcomes Research that was held in May, Woodcock reviewed the complexities of risk management efforts. She remarked that reaching the goal of maximizing benefits and minimizing risks of drugs on the market involves preventing inappropriate prescribing, recognizing possible drug–drug interactions, encouraging correct patient compliance, and reducing dispensing errors. Certain high-risk products may require behavior intervention, particularly for high-risk populations such as pregnant women.

However, evaluating benefits and comparing them with foreseeable risks during drug development is difficult, she noted, because comparatively few patients are exposed to a new drug during the premarket testing phase. The testing process thus provides little information about infrequent adverse events. In addition, predicting benefits is difficult because data from randomized controlled trials lack generalizability. Once on the market, however, a drug may emerge as less safe if it is used in ways that decrease expected benefits or that increase risks—or if actual risks turn out to be greater than predicted risks.

Who's who in FDA risk management

Steven Galson, CDER deputy director, came to FDA last year to oversee CDER risk management initiatives. He has extensive experience with public health and risk management concerns, most recently as director of the Office of Science Coordination and Policy, Office of Prevention, Pesticides, and Toxic Substances, at the US Environmental Protection Agency (EPA). Previously he was the scientific director of EPA's Office of Children's Health Protection, where he organized the first national conference about preventable causes of children's cancer. Until June 1997, Galson was the chief medical officer at the Department of Energy (DOE), a position that involved him in public-health questions concerning nuclear weapons. Earlier, Galson conducted epidemiologic studies at the National Institute for Occupational Safety and Health at the Centers for Disease Control (CDC) and Prevention, was an environmental health officer in New York state, and worked overseas on refugee emergencies. Galson has a medical degree from Mt. Sinai School of Medicine and an MPH from Harvard University.

Paul Seligman, director of CDER's Office of Pharmacoepidemiology and Statistical Science, previously worked with Galson at DOE and has extensive experience in epidemiology and health surveillance. During the seven years before coming to FDA, Seligman served as DOE deputy assistant secretary for the Office of Health Studies. As a Congressional Fellow for two years, he advised Sen. Paul Wellstone about health policy. Before that position he was a medical epidemiologist at CDC's National Institute for Occupational Safety and Health. He has been a teacher and a Peace Corps volunteer and has a medical degree from the University of California and an MPH from the University of Michigan.

Seeking new tools

FDA officials are particularly concerned that traditional risk management strategies do not appear sufficient to deal with current safety problems. At the CDER public hearing, agency officials noted that several drugs were withdrawn from the market because FDA and the sponsor were unable to convince prescribers and patients to use the therapy appropriately. Too frequently, physicians prescribe drugs with known risks to inappropriate patients, in inappropriate dosages, and in the presence of other drugs or treatments that are likely to produce harmful interactions. Currently available techniques for preventing such risky behavior—e.g., changing labels, adding black-box warnings, requiring medication guides, and sending out "Dear healthcare professional" letters—often fail to gain the desired response from physicians and the public. Such situations force FDA and the manufacturer to withdraw the product from the market—a move that all sides agree reflects a failure of risk management efforts. Last year, Bayer withdrew the cholesterol-lowering drug Baycol (cerivastatin) from the market in response to reports of sometimes-fatal muscle reactions. Reports of serious bronchospasm reactions led Organon to withdraw the anesthesia drug Raplon (rapacuronium).

Determined to overcome these setbacks, FDA is looking for new approaches to reducing risk associated with prescription drugs. CDER has worked with manufacturers to develop an expanded toolbox of risk management activities. These procedures include

- requiring patients to sign agreements or informed consent forms indicating that they have been informed about risks associated with the therapy and will follow certain procedures to avoid unsafe practices
- controlling product distribution, often through the use of centralized warehouses and a limited number of pharmacies
- educating, certifying, and qualifying healthcare professionals who prescribe the drug
- keeping registries of patients, physicians, and pharmacies who participate in a risk management program
- listing toll-free numbers on product labels to facilitate adverse-event reporting
- requiring manufacturers to undertake Phase IV studies plus additional surveillance programs to ensure that patients and prescribers adhere to program requirements
- implementing packaging strategies such as special blister packs to help ensure that a patient takes the specified amount of medication at specified intervals. Packages that hold only a limited supply of a drug require the patient to consult a physician before obtaining a refill. High-risk medications can be made available in special packages with highly visible warnings and cautions.

Manufacturers adopt controls

Several of these strategies have been implemented in programs to keep products causing special risk concerns on the market. To prevent the use of Thalomid (thalidomide) by pregnant women, Celgene has established a managed-distribution system. The system requires all patients, prescribers, and pharmacies using or managing the product to

register with the company and review educational materials about the drug. Patients must sign an informed consent form, and prescribers must attest that they have provided safety information to the patient. The manufacturer distributes the drug from a single warehouse and sends it in small lots directly to a pharmacy to avoid diversion. Increased use of the drug for off-label oncology treatment, however, may overwhelm this limited distribution system.

Roche's risk management program for Accutane (isotretinoin) has a similar goal. The company requires young female patients to take pregnancy tests and use two forms of birth control. It dispenses only one-month supplies, includes informed-consent information in a package insert, and requires a physician to put a sticker on the written prescription to indicate adherence to the program.

The Drug Safety and Risk Management advisory subcommittee, established last year to advise FDA about product-specific and overall drug safety issues, is on board to help FDA assess the need for risk management strategies. The panel held its first meeting in April to weigh strategies that could allow GlaxoSmith-Kline's irritable bowel syndrome therapy Lotronex (alosetron HCl) to return to market. Glaxo withdrew the product in November 2000 following serious adverse-event reports of ischemic colitis. At that time, the manufacturer and FDA failed to agree about what risk management tools were necessary to ensure safe use of the product by patients. In April the risk advisory panel, together with representatives of FDA's Gastrointestinal Drugs Advisory Committee, recommended that FDA make the drug available to patients with certain marketing restrictions.

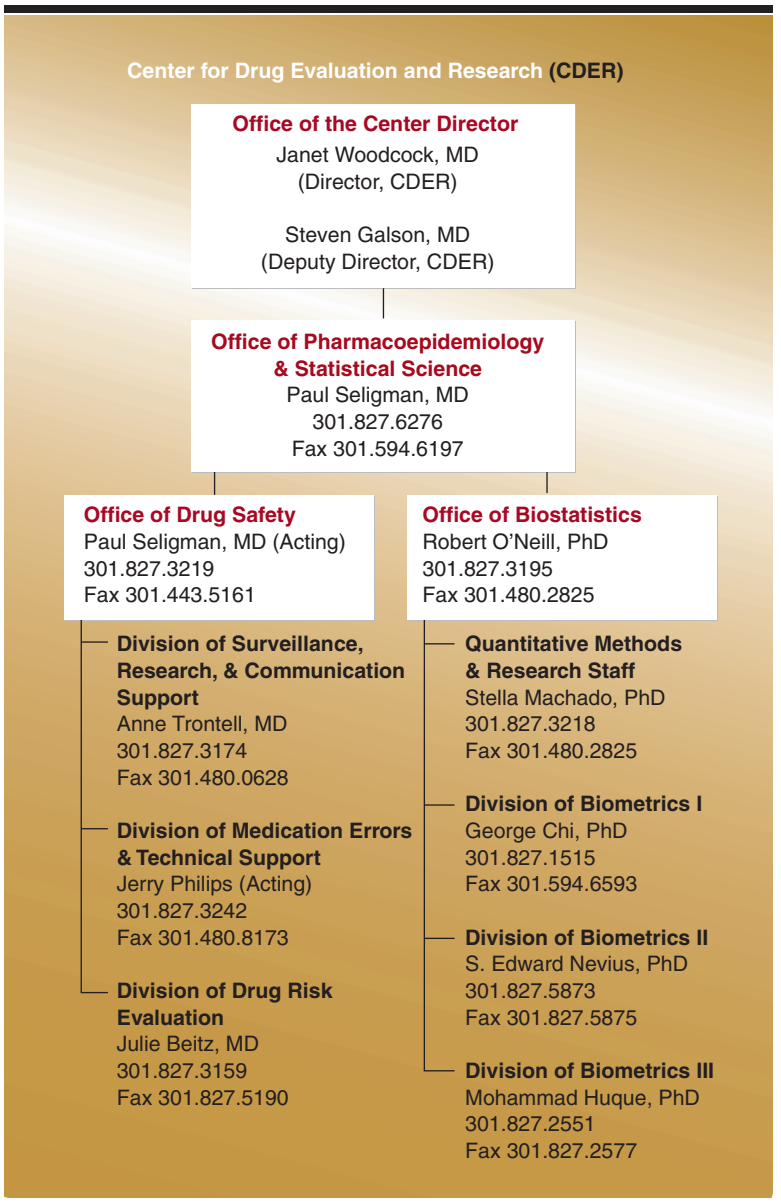

Figure 1: CDER's Office of Pharmacoepidemiology & Statistical Science divisions and directors.

After further negotiations, FDA approved Lotronex for market on 7 June under Subpart H regulations, which permit rapid withdrawal from the market by the agency if the company's risk plan fails to ensure safe use. Glaxo agreed to a restricted marketing program to limit use of the drug to patients with severe symptoms who do not respond to other treatment. The risk management program permits prescribing only by physicians who enroll in an educational program, agree to inform patients of risks, and pledge to report serious adverse events. Participating physicians must apply stickers to written prescriptions to indicate to pharmacists that they adhere to the program. Glaxo committed to conducting several Phase IV clinical trials to test various doses and clinical effects as well as extensive epidemiological studies to assess whether doctors and patients follow the program. Glaxo will issue a medication guide for patients in which it will recommend a lower starting dose of 1 mg per day. At present the company is establishing patient and doctor registries, which it had considered unnecessary.

Changing drug development

FDA's heightened emphasis on identifying a drug's risk factors before market approval is prompting manufacturers to assess safety issues more extensively in clinical trials. This change involves developing a safety profile of the test therapy early in the clinical study process to analyze available safety data and to gain a full understanding of disease epidemiology. The sponsor then could estimate known and potential risks and describe them in safety plans filed in its new drug application (NDA). Before it approves a new drug, FDA must assess the associated disease epidemiology, risk management tools suitable for addressing the drug's known and potential risks, suggestions from the manufacturer for Phase IV epidemiology studies, and proposals for targeted postapproval surveillance.

Even more significant changes are emerging for the postmarketing period. The new prescription drug user fee program (PDUFA III) provides additional funds for CDER postmarket surveillance activities. In addition to reviewing sponsor risk management plans upon a drug's approval, FDA will gain resources to monitor new drugs more closely during the peri-approval period, which is two years following launch for standard drugs and three years for those deemed more risky. During this monitoring period FDA will assess the effects of various risk management strategies and the results of Phase IV studies. PDUFA also will support an expansion of FDA adverse-event tracking and assessment, which will be handled by agency epidemiologists and statisticians. As part of this process, FDA will expect to receive more information from sponsors about whether the drug is being used according to label.

Another FDA initiative is aimed at providing timely updated safety information on product labels. FDA issued a proposed rule on 3 May that would require manufacturers to submit labeling text electronically to FDA with applications for new drugs, generics, biotech therapies, supplements, and annual reports. This rule would greatly facilitate FDA approval of new and revised product labels and eventually support an electronic information system with full drug-labeling information that could replace paper package inserts. The initiative also would provide a more useful database about drug safety that would enable pharmacists to provide consumers with the most-current labeling information.

To facilitate development of this program, several manufacturers are participating in a paperless labeling pilot pro-

gram sponsored by the Pharmaceutical Research and Manufacturers of America. A test this summer will transmit electronic labeling information to a group of pharmacies that would then print paper labels as needed. The pilot is designed to determine system capabilities, any resulting difficulties at pharmacies, cost savings to manufacturers, and improvement in information dissemination to the public.

Risks and resistance

Even though these initiatives should make it easier for health professionals to identify safety problems and to communicate this information to patients, many pharmacists and physicians find the recent proliferation of product-specific risk management programs burdensome and are displaying some resistance to these efforts. In addition to complaining about more recordkeeping and paperwork, pharmacists oppose programs that limit product distribution to select outlets, and physicians don't like policies that allow only certain specialists to prescribe a therapy.

Legal experts question whether FDA proposals to limit who can prescribe or dispense an approved drug interfere with state authority to regulate the practice of medicine and of pharmacy. In addition, requirements for patients to provide personal health information for registries may raise patient privacy problems. Any mandate forcing patients to sign consent forms or join registries to obtain an approved drug may prompt legal challenges about right of access and coercion.

Extensive risk management programs also can add considerably to manufacturing costs, particularly if the program requires patient registration or changes in packaging and labeling. Glaxo agreed to reduce the initial dose for Lotronex to 1 mg once daily but balked at a proposal to offer a ½-mg tablet because that move would require the company to completely overhaul its production line.

An added concern for manufacturers is that tight restrictions on distribution may

OPSS oversees pre- and postmarket safety issues

CDER established the Office of Pharmacoepidemiology and Statistical Science (OPSS) on 1 January 2002 by combining several functions into one office. The Office of Drug Safety (ODS) oversees postapproval surveillance, adverse-event reporting, medication errors, and risk evaluation. The Office of Biostatistics (OB) analyzes statistical data in new drug applications and in postmarketing reports to assess safety and risk issues.

ODS was formed by combining the former Office of Postmarketing Drug Risk Assessment with FDA's MedWatch program (from CDER's Office of Training and Communications) and patient labeling and communications functions such as MedGuide development (from the Division of Drug Marketing, Advertising, and Communications [DDMAC]). OPSS director Paul Seligman currently is serving as ODS acting director following the recent departure of former OPDRA director Peter Honig. Martin Himmel is ODS deputy director, Jerry Phillips is ODS associate director for medication error prevention, and Kathleen Bongiovanni is associate director for regulatory affairs.

ODS activities are handled by the following three divisions:

Division of Drug Risk Evaluation (DDRE). DDRE, which is headed by Julie Beitz, is a group of safety evaluators that looks for and assesses safety signals for all marketed drugs and works with CDER medical reviewers to understand the context of such safety information. DDRE's epidemiology staff reviews protocols for Phase IV studies and assesses other risk management strategies, including patient registries and restricted distribution systems. This group estimates the effects of safety signals on public health by evaluating computerized databases and published literature.

Division of Surveillance, Research, and Communications Support (SRCS). SRCS, which is headed by Anne Trontell, manages resources, risk communication, and outcomes research. This includes FDA's MedWatch program and other risk-communication activities such as the development of MedGuides, patient package inserts, and pharmacy guides, responsibilities that were transferred to ODS from DDMAC. It also handles international postmarketing safety issues, a duty that involves communicating drug risk information to foreign regulatory agencies. SRCS will oversee planned expansion in the use of drug safety and epidemiologic data resources, including drug use data from industry data firms, inpatient drug use databases, and insurance claims databases.

Division of Medication Errors and Technical Support (DMETS). DMETS, whose acting director is Jerry Phillips, oversees premarket review of all proprietary names and labels to reduce the potential for medication error. This staff reviews and analyzes all medication-error reports filed with the agency and also provides information technology support for ODS.

Headed by Robert O'Neill, OPSS also includes OB, which was formerly part of CDER's Office of Review Management, now the Office of New Drugs. OB has not changed significantly as a result of this shift. Its three divisions of biometrics, headed by George Chi, S. Edward Nevius, and Mohammed Huque, work with new drug medical review staffs. These statisticians review problems related to clinical study design, data handling, and analysis of data that arise during the review of INDs, NDAs, abbreviated NDAs, and supplements. This responsibility involves evaluating the mathematical and statistical methods and inferences drawn from data submitted by drug sponsors. In many cases, the statisticians are called on to address specific challenges related to study design or interpretations such as the use of meta-analysis or adjusting for covariates. A Quantitative Methods and Research staff headed by Stella Machado supports the design and assessment of complex safety protocols.

OB is becoming increasingly involved with the design and assessment of Phase IV studies and postapproval safety issues. As CDER focuses more on quantitative risk assessment, this function crosses biometry and epidemiology. Moving OB to OPSS aims to facilitate such efforts.

generate gray- and black-market sales of a product, pointed out attorney Daniel Krakov at the DIA risk management workshop. Although many manufacturers have agreed to adopt FDA proposals for complex risk management programs, Krakov questions whether sufficient research indicates that such systemic control efforts are appropriate or have desired effects.

Does risk management work?

CDER's ODS hopes to answer such questions, says Anne Trontell, director of the ODS Division of Surveillance, Research, and Communication, who acknowledges that the task is challenging. The effects of risk management initiatives may be measured by a decrease in the number or rate of adverse events, reduced severity of adverse events, or expanded knowledge about adverse-event risks, Trontell explained at the DIA conference. She observed that it is particularly difficult to assess whether risk communication is occurring and whether tracking and certification processes operate effectively. The problem is that risk management programs incorporate many components, specific interventions are not standardized, and so far manufacturers and regulators have limited experience with these programs.

A decline in the number of adverse-event reports may not be a reliable indicator of risk management success, Trontell points out. Such a decline could result from expansion or improvement in FDA's Adverse Event Reporting System or expanded adverse-event reporting by hospitals and prescribers. Conversely, a general decrease in adverse-event reports may reflect a decline either in the number of new drugs approved by FDA or in CDER's approval of more waivers that allow manufacturers to reduce adverse-event filings on nonserious and labeled adverse events. Publicity about drug risks may boost adverse-event reporting just as limited awareness may drive down public filings.

Manufacturers are urging FDA to adopt a flexible approach to risk management and to avoid a one-size-fits-all policy. At the same time, there is a strong push from all sides for a degree of standardization in risk management tools and strategies to develop international standards for defining serious adverse events. Another aim is to obtain uniformity in the design and scope of patient and physician registries so that information requests are similar.

FDA is deliberating the suggestions and proposals presented at the May public hearing and those submitted subsequently by interested parties. CDER plans to test some of the ideas as it develops more risk management programs with manufacturers and will weigh the need for additional guidance or other policies to further these goals. The agency also is finalizing a risk management white paper. This report will describe future initiatives and a risk research agenda involving FDA and the Centers for Education and Research on Therapeutics, which are working on numerous projects involving evaluation and communication of the benefits and risks of medical therapies.

Congress wants to determine whether increased attention to risk assessment and management enhances the safe use of medical products, and other government watchdogs will be examining risk management programs. Risk management is here to stay, and it promises to bring significant changes in operations for pharmaceutical manufacturers. **PT**