BY ELISABETH PENA

risky business

Gene **Guselli**

Risk management is an area that is going to morph for a while — we are right in the thick of it. This is an area that holds an enormous amount of potential for all involved, and the hope is that the industry embraces it rather then defends against it.

THE PHARMACEUTICAL INDUSTRY FACES MORE INHERENT RISKS AND HIGHER STAKES THAN ALMOST ANY OTHER INDUSTRY because its products impact patient safety and well-being. **INTENSIFIED PUBLIC AND MEDIA SCRUTINY ABOUT MEDICATION ERRORS AND DRUGS BEING PULLED OFF THE MARKET HAVE INDUSTRY EXECUTIVES, WITH GUIDANCE FROM THE FDA, WORKING TO ASSESS THE RISKS AND DEVELOP PROGRAMS TO ENSURE THE SAFETY OF ALL PROCESSES.**

risk permeates almost every area and discipline within the pharmaceutical industry. So the scope and opportunities for risk-management programs are vast. While companies have always worked to ensure the safety of their products, regulatory authorities around the globe are requiring more formalized strategies to minimize safety risks throughout the product life cycle.

Recent guidances from the Food and Drug Administration have outlined activities around the general topic of risk management. These include the 2002 Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach and the more recent guidances that focus around the narrower topic of product-specific risk management (pharmacovigilance) as directed by the Prescription Drug User Fee Act III (PDUFA-III). (See box on page 42 for more detailed information.)

"Companies have to pay attention to both guidances, recognizing, however, that the guidelines are addressing different areas of risk," says Frances E. Nolan, VP and consultant at Taratec. "If a company manufactures and sells drugs, it needs to understand the intent of both initiatives."

The industry's very business, developing human therapeutics, means risk management must be front and center of operations across the board, from assessing the benefits and risks of a product for the patient to the risks associated with the development and marketing of a drug.

"Key considerations in the pharmaceutical industry, and the driving force behind the FDA's charters, are potential risks to patient safety, product quality, and data integrity, as well as risks associated with patient privacy," Ms. Nolan says. "As with all industries, pharmaceutical companies also face financial, public expectation, and other business operations-related risks, as well as risks related to noncompliance with nonindustry-specific U.S. regulations, such as Sarbanes-Oxley, the Health Insurance Portability and Accountability Act, as well as non-U.S. and other international regulations and guidelines, such as the European Union Data Directive 95/46 related to the processing of personal information."

According to Jeffrey E. Fetterman, president and CEO of ParagonRx, the Institute of Medicine report on patient safety, To Err is Human: Building A Safer Health System, which was published in 1999, sparked much public discussion and ultimately FDA action.

"This landmark publication showed an excess of medical errors and poor patient outcomes associated with a variety of medical errors," he says. "It really galvanized public attention on patient safety as a major concern, and some of the FDA action may be a response to the increased public attention."

Although risk management is not a new concept for the industry, the recent attention to the topic has created some confusion.

"The term risk management can be ambiguous," Mr. Fetterman says. "Many assume when there is talk of risk management that it refers to mitigating the risks of adverse events of pharmaceuticals, but there are a lot of other ways to think of risk. There is management of legal risks, drug-development portfolio risk management, and the FDA itself is looking at risk management of its own internal process. As there are many ways to define risk management, it is important to clarify definitions in any discussion."

Sam Holtzman, Ph.D., chairman, president, and CEO of Rosa Pharmaceuticals Inc., says that the FDA's recent initiatives are a response to, and an institutionalization of, a risk-management trend that industry leaders have advocated for years.

"These initiatives are a positive force, and,

in recent years, the FDA has been supportive and adoptive of the trend," Dr. Holtzman says.

Leyna Mulholland, Ph.D., senior manager of pharmaceutical development at Merck & Co., says drugs have always had to be efficacious, as well as safe, and that the FDA's risk-management initiative reiterates the focus on those components.

"In my department, risk management is part of the project-development plan," she says. "It is part of the contract, so as we plan for drug development, risk assessment, and risk management have to be part of that plan."

a considered approach

Pharmaceutical companies have long performed risk-assessment and risk-minimization activities for products during development and marketing that meet the Federal Food, Drug, and Cosmetic Act and the FDA implementing regulations for routine risk assessment and risk minimization, FDA regulations regarding spontaneous adverse event reporting, and FDA-approved professional labeling.

"Risk management has always been around but it has been more reactive in the past," says Matthew Reynolds, Ph.D., senior director of risk management and safety at MetaWorks. "Now with the recent FDA guidances, companies need to be more proactive in thinking through risk-benefit assessment and comprehensive risk management before filing a NDA."

David Lilienfeld, M.D., senior director of drug safety at InterMune, also says the FDA's interest in risk management is not new, but it hadn't been broadcast as a policy focus.

"Consider several examples of risk-management plans implemented since the 1980s, such as the Clozaril risk-management pro-

Selected Risk-Management Programs

DRUG/INDICATION	RISK FACTOR	PROGRAM	KEY PROGRAM ELEMENTS
ACCUTANE (isotretinoin) Severe acne	Teratogenicity	S.M.A.R.T. (System to Manage Accutane Related Teratogenicity)	Physician/patient/pharmacist registration and qualification • Letter of understanding (prescriber checklist) • Limited distribution (qualification stickers, no refills, 30-day supply, seven-day written only Rx) • Mandatory patient Accutane survey • Patient consent form • Educational material • Pregnancy prevention program (patient counseling) • Medication guide
FORTEO (teriparatide [rDNA origin] injection) Osteoporosis	Osteosarcoma	Forteo Customer Care Program	Phased introduction; restricted initial marketing;limited salesforce • Physician education program • Patient registry • Educational materials; newsletters • No DTC advertising • Patient starter kit • Medication guide • Post-approval 10-year patient surveillance program
LOTRONEX (alosetron) Severe diarrhea predominant IBS	Serious gastrointestinal adverse events	Prescribing Program for Lotronex	Physician attestation • Patient-physician agreement • Limited distribution (special packaging, qualification stickers, no refills) • Medication guide • Patient survey • Educational materials
MIFEPREX (mifepristone) Pregnancy termination	Abuse (Social implications)	Patient Selection and Follow-up Drug Security	Physician registration/qualification • Patient agreement • Restricted distribution (central drug dispensing, special packaging, no refills) • Patient monitoring • Medication guide
PLENAXIS (abarelix) Advanced prostate cancer	Systematic allergic reactions	PLUS Program (Plenaxis User Safety Program)	Physician attestation • Educational programs for physicians, patients, hospital pharmacists • Restricted distribution (central drug dispensing) • Patient monitoring • Patient agreement
THALOMID (thalidomide) Erythema nodosum leprosum	Teratogenicity	S.T.E.P.S.(System for Thalidomide Education and Prescribing Safety)	Physician/patient registry • Mandatory contraception counseling • Physician/patient education • Patient informed consent form • Patient/prescriber mandatory enrollment and follow-up survey • Pharmacy registration • Restricted distribution (no refills, four-week supply, seven-day written only Rx)
TIKOSYN (dofetilide) Arrhythmia	Torsades de pointes	T.I.P.S. (Tikosyn in Pharmacy System)	Physician/institution registration/certification (Tikosyn Education Distribution) • Patient monitoring • Restricted distribution (pharmacy enrollment requirements, stamp required on each Rx)
TRACLEER (bosentan) Pulmonary arterial hypertension	Hepatoxicity	TAP (Tracleer Access Program)	Patient enrollment • Restricted distribution (specialty distributor) • Medication guide
XYREM (sodium oxybate) Cataplexy	Abuse (social implications)	Xyrem Success Program	Physician/patient education verification • Physician/patient registry • Restricted distribution (central pharmacy) • Special prescription forms • Medication guide • Postmarketing patient evaluation

Source: ParagonRx, Wilmington, Del.(Information was retrieved through various publicly available sources, i.e.,product Websites, company Websites, FDA documentation). For more information,visit paragonrx.com.

Frances **Nolan**

Companies have to pay attention to both FDA guidances, recognizing, however, that the guidances are addressing different areas of risk.

Dr. Louis **Morris**

The FDA has done a terrific job of getting people to focus on risk management in a systematic way. The agency has changed the way the industry thinks about risk management.

gram," he says. "This program demonstrated the safety of Clozaril after six months of use rather than the one year originally thought to be the period of risk for agranulocytosis."

Clozaril, a Novartis therapeutic, is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard treatment. Since its introduction in 1990, Clozaril has only been available through a strict monitoring and distribution system to detect the early onset of agranulocytosis, a condition in which there is an insufficient number of white blood cells called neutrophils or granulocytes, which can lead to infections. The program includes a national registry, which was developed in response to a FDA mandate to ensure the safety of patients treated with Clozaril.

Gene Guselli, cofounder, president, and CEO, of InfoMedics Inc., believes that the industry has the opportunity to rebuild credibility by evaluating its risk-management processes.

"This is a real softball being thrown by the FDA to the industry," he says. "If pharma companies can position themselves and their programs appropriately, this could be a very positive public-relations endeavor for them."

Experts also point out that the recommendations presented in the FDA's Draft Guidance for Industry Development and Use of Risk Minimization Action Plans (RiskMAP) focus on situations when a product may pose an unusual type or level of risk.

The term RiskMAP refers to a strategic safety program designed to meet specific goals and objectives to minimize known risks of a product while preserving its benefits. A RiskMAP targets one or more safety-related health outcomes or goals and uses one or more tools to achieve those goals.

Examples of RiskMAP goals include recommendations that patients on "x" drug should not also be prescribed "y" drug, or fetal exposures to "z" drug should not occur. Although it might not be possible to ensure that absolutely no one on "x" drug receives "y" drug, the FDA believes that the goal should reflect the ideal outcome of the RiskMAP.

To develop a RiskMAP, companies need to gain a complete understanding of the potential risks associated with a particular product and explore all possible interventions. Based on this understanding, they must then establish clear goals for what the RiskMAP should accomplish. Other points laid out by the FDA's guidance regarding RiskMAPs include that all stakeholders need to be addressed to ensure that they understand the risks as well as the benefits of the product. Potential elements include

Choose Your Weapons

www.challengeyourdata.com

Challenge Your Data

Challenge your lab, IVR, EDC and eDiary data to work together (even when your IT and Data Management departments are fighting different battles). etrials' products make it simple to aggregate data feeds from different sources. You can easily report across your entire study instead of just a portion of it. Visit www.challengeyourdata.com for real-life examples of etrials' integrated product suite. Or call us at 866-etrials (387-4257) in the US or +44 (0) 1795 479041 in Europe.

etrials

SUPERIOR TECHNOLOGY WITH A HUMAN TOUCH

ELECTRONIC DATA CAPTURE
INTERACTIVE VOICE RESPONSE
ELECTRONIC PATIENT DIARIES
WWW.ETRIALS.COM

targeted education and labeling, reminder systems, and/or performance linked access systems.

Once the goals are established and the program is in place, there also should be a transparent evaluation of the effectiveness of the program to ensure that all of the goals are being met. The program should then be revised over time to update the interventions, thereby maximizing effectiveness. This assessment provision is one that Dr. Reynolds believes is a very important part of the guidance and will have a positive impact on public health.

"One important thing that has been lacking in the past is the actual evaluation of all the risk-management interventions," he says. "One of the major benefits in this current risk-management evolution is that different interventions, whether it be a Dear Doctor Letter, a patient-education program, a Website, or patient-identification bracelets, will all need to be evaluated as to their effectiveness. This has not been consistently conducted in the past; now as companies put RiskMAPs in place they will need to determine whether these measures are effective in reducing the risk and maximizing the benefit of the drugs. This is significant progress for public health."

Ensuring that a drug is used safely and is not associated with a higher than expected amount

Sound Bites from the Field

PHARMAVOICE ASKED INDUSTRY EXPERTS WHAT THE CHALLENGES OR OBSTACLES ARE TO IMPLEMENTING AN ENTERPRISEWIDE RISK-MANAGEMENT PLAN.

MELANIE BRUNO is VP of Global Regulatory Affairs at Kendle International Inc., Cincinnati, which is one of the world's leading global clinical-research organizations, delivering clinical-development solutions to help the world's biopharmaceutical companies maximize product life cycles and grow market share. For more information, visit kendle.com.

"Challenges to implementing an enterprisewide risk-management plan include completing a thorough assessment of potential product risks and determining which types of programs can address the risk needs. A risk-management plan should be comprehensive so that risk can be evaluated, managed, and measured at the patient, pharmacy, physician, and company levels. Implementation obstacles include availability of educational materials, analytical processes for evaluation, and human resources."

MONIKA PIETREK, PH.D., M.D., M.SC., is Senior VP, Global Medical and Safety Services, at PRA International, McLean, Va., one of the world's leading clinical-development organizations. For more information, visit prainternational.com.

"Multidisciplinary expertise, unbiased assessment, and effective communications to all stakeholders are key components to successfully managing the benefits and risks of a pharmaceutical compound. Companies need to be committed to scientific excellence and unquestionable ethics, eliminate functional barriers, provide adequate resources, and plan short-term as well as long-term risk minimization. Risk management is a continuum over the entire product life cycle. Low staff turnover and an integrated approach between research, development, and marketing will contribute to the successful implementation of risk-management plans."

JILL WADLUND is VP, Chubb & Son, and Life Sciences Casualty Manager for Chubb Commercial Insurance, Warren, N.J., a part of the Chubb Group of Insurance Companies, which form a multibillion dollar organization providing property and casualty insurance for personal and commercial customers worldwide. For more information, visit chubb.com.

"The simple fact is that risk lurks around every corner and is unavoidable. It stems from virtually every aspect of an organization, including research, clinical, manufacturing, marketing, IT operations, products, property, employees, and relationships with business partners, competitors, and regulators. Clearly, there are numerous benefits to the bottom line by coordinating risk management across the entire organization. But doing it is easier said than done. Implementing enterprise risk management requires a pharmaceutical company to identify, analyze, quantify, and compare all of its exposures emanating from operational, financial, and strategic activities. It requires the constant monitoring of a changing risk profile as the company evolves from research to trials to product manufacturing and marketing and branches out into new markets around the world. Although the risk profiles of every organization will vary, risk managers in the life-sciences community may find that some of the most serious risks to the bottom line include research delays, trade secret theft, latent product exposures, sales and marketing practices, clinical-trial practices, and international concerns. Unfortunately, since even the best risk-management practices may fail to eliminate all exposures, senior managers from such areas as finance, regulatory affairs, legal, investor relations, and public relations must prepare an enterprisewide crisis management and business continuation plan. A well-thought-out plan, which contemplates all potential disasters throughout the organization and all appropriate responses, can make the difference between never recovering from a major loss and continuing operations with minimal disruption."

Theodore **Frank**

Pharma has substantially higher product development risks. That forces the industry to have a much higher level of awareness and a much more sophisticated approach to risk management than virtually any other industry.

Dr. Matthew **Reynolds**

There is very little downside to proactive risk management because it shows that a company has thought through all the risks of the drug through examination of clinical trials and has done due diligence by understanding the effects of other drugs in the class.

of adverse events or safety issues is a continual process.

"The management of risk begins in the clinical-development process and extends through the life of the drug, including post-marketing," Dr. Reynolds says. "For a variety of reasons, it is especially critical that the risk-management plan is continually being evaluated and the risks are continually being assessed in that initial year or two after launch."

Many believe patient treatment will be vastly enhanced by the FDA guidances.

"During the next decade, it seems likely that many compounds deemed too unsafe for the marketplace will be approved for marketing because they have appropriate risk-management programs," Dr. Lilienfeld says. "It's important to note, however, that risk management is not synonymous with risk minimization."

plan of action

Many parts of a company's business are affected by the decision to focus on risk management. From a general companywide perspective, Ms. Nolan has found that a life-science company's risk-management plan needs to address the identification, assessment, and prioritization of potential business and regulatory compliance risks; the development and implementation of risk management and risk mitigation tools and techniques that are appropriate for the risks thus identified; and the ongoing monitoring of the effectiveness of the risk-management plan.

"Risk-management planning and effective governance in this industry provides an opportunity for all disciplines, including compliance experts, business representatives, and support organizations such as finance and IT to work together to develop a justified and documented approach to dealing with risk," she says.

"It is a problem when companies look at risk management myopically, tackling a specific process in manufacturing or in R&D or in sales and marketing," says Theodore Frank, CEO of Axentis Inc. "Each of the silos develops a unique way of managing its processes, which end up being very inconsistent. The goal for companies should be to create a consistent operational approach for managing all these processes, whether it is a R&D process or a sales and marketing process. A consistent operational approach is essential

Trim the Fat

www.challengeyourcro.com

Challenge Your CRO

Do you like paying for things you don't need? That's exactly what you're doing if you're not using EDC to maximize the efficiency of your clinical trial. Challenge your CRO to join the twenty-first century. Visit www.challengeyourcro.com for real-life examples of EDC efficiencies, savings, and ROI. Or call us at 866-etrials (387-4257) in the US or +44 (0) 1795 479041 in Europe.

etrials

SUPERIOR TECHNOLOGY WITH A HUMAN TOUCH

ELECTRONIC DATA CAPTURE
INTERACTIVE VOICE RESPONSE
ELECTRONIC PATIENT DIARIES
WWW.ETRIALS.COM

The FDA'S Risk-Based Initiatives

TOGETHER, RISK ASSESSMENT AND RISK MINIMIZATION FORM WHAT THE FDA CALLS RISK MANAGEMENT.

Risk management is an iterative process of assessing a product's benefit-risk balance, developing and implementing tools to minimize its risks while preserving its benefits, evaluating tool effectiveness and reassessing the benefit-risk balance, and making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's life cycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

PDUFA III-related risk-management guidance

In the context of PDUFA III, the FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk-management activities for drug and biological products. Specifically, the FDA issued three concept papers. Each paper focused on one aspect of risk management, including conducting premarketing risk assessment, developing and implementing risk-minimization tools, and performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments.

On May 5, 2004, the FDA issued for comment three guidance documents on risk-management activities. FDA officials are currently reviewing comments to address in a final guidance.

The first document, Premarketing Risk Assessment, provides guidance on good risk-assessment practices during the development of prescription drug products, including biological drugs. This document discusses the generation, acquisition, analysis, and presentation of premarketing safety data.

The second document, Development and Use of Risk Minimization Action Plans, provides guidance on the development, implementation, and evaluation of risk-minimization action plans for prescription drug products, including biological drugs. In particular, it gives guidance on initiating and designing plans to minimize known risks (i.e., risk-minimization action plans or RiskMAPs), selecting and developing tools to minimize those risks, evaluating and monitoring tools and RiskMAPs, and submitting the recommended components of a RiskMap to the FDA.

The third document, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, focuses on postmarketing risk assessment. It provides guidance on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drugs (excluding blood and blood components). Specifically, it provides guidance on safety signal identification, pharmacoepidemiologic assessment and safety signal interpretation, and pharmacovigilance plan development.

GMP-related risk-management guidance

In August 2002, the FDA launched a two-year initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach. This initiative outlined a science and risk-based approach to product quality regulation incorporating an integrated quality systems approach.

The FDA oversees the quality of drug products using a two-pronged approach involving review of information submitted in NDAs, as well as inspection of manufacturing facilities for conformance to requirements for current Good Manufacturing Practice (cGMP).

This guidance was part of an initiative to modernize the regulation of pharmaceutical manufacturing and product quality, which aims to ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science and do not impede rapid adoption of new technological advances. The initiative also promises to enhance safety and quality in drug manufacturing while increasing efficiencies.

The guidance, which applies to human drugs, biologics, and veterinary drugs, has several objectives: to encourage the early adoption of new technological advances; to facilitate industry application of modern quality management techniques, including implementation of quality systems approaches to all aspects of pharmaceutical production and quality assurance; to encourage risk-based approaches that focus both industry and agency attention on critical areas; to ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science; and to enhance the consistency and coordination of the FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the agency's business processes and regulatory policies concerning review and inspection activities.

The cGMP initiative was made an important component of the science-based risk-management goal in the FDA's August 20, 2003, Five-Part Strategic Action Plan to Protect and Advance America's Health.

To ensure that a risk-management approach is applied to FDA inspectional resources, the FDA is developing a quantitative risk-based site-selection model for use in choosing sites for inspection. This model, which was slated to be piloted for human drugs in October 2004, helps the FDA predict where its inspections are most likely to achieve the greatest public health impact and includes risk factors relating to the facility (such as the compliance history) and to the type of drugs manufactured at the facility. It also includes risk factors relating to the manufacturing processes and the level of process understanding.

The FDA also has developed action plans for the review and revision of field compliance programs to incorporate risk-based approaches to improve transparency and guide FDA investigators in conducting inspections. Other compliance programs for revision toward a more risk-based approach have been identified, including the preapproval inspection program and active pharmaceutical ingredients (API) program.

Source: The Food and Drug Administration, Rockville, Md. For more information, visit fda.gov.

Linda **Sadler**

Pharmaceutical risk management deals with issues of patient safety and well-being. That makes the stakes very high. Pharma companies will need to learn how to optimize RiskMAPs under a microscope of intense scrutiny by both the public and the FDA.

Dr. Gerald **Faich**

The methods risk management uses go beyond traditional product labeling and education. The main challenge is to develop effective tools in a manner that does not promote unapproved use and does not stimulate product use by improper incentives for prescribing physicians.

because fragmentation results in additional costs and in poor performance. Most importantly, there is little visibility on an enterprisewide basis into how risk management is being handled across the organization."

For risk management relating to product development, Dr. Mulholland highlights four major areas of concentration for Merck.

"From the early phases to the late phases of drug development, there are so many areas that we could tackle, but most important are early formulation development, safety assessment, global clinical-trials development, and the postmarketing process," she says.

Once the areas are identified, next should be the key components for a plan. Gerald Faich, M.D., MPH, chief medical officer of BBCI, and a former director of the Office of Epidemiology and Biostatistics at the FDA, outlines four key components: first, risk assessment, defining what risks are to be addressed and how often these occur; second, intervention design, deciding on the tools or interventions to be used to reduce the risk, such as proactive registration, reminder systems, or performance-linked interventions, such as required blood testing; third, implementation of the intervention; and fourth, evaluation against preset objectives.

finding a **balance**

When the need to develop a RiskMAP is determined during a company's risk-assessment process, a delicate balance between burden and benefit must be achieved. Programs that are too involved may negate the beneficial effects intended.

"The question is how does a company intervene when there is a known or suspected risk?" says Louis A. Morris, Ph.D., president of Louis A. Morris & Associates Inc. "There needs to be a way of modifying behavior in a way that doesn't cause a huge burden for the healthcare professionals or patients involved and that provides a beneficial impact to risk management, but does not block access to the medication in general. Coming up with the right combination of interventions and learnings is important."

Take It Easy

+

+

Challenge Your Technology

What do a faucet, a light switch and PDA have to do with collecting data? Each represents etrials' belief that software should be simple to implement, easy to use and quick to see ROI. Challenge your technology to work flawlessly in your next clinical study. For real-life examples of investigator praise for etrials' integrated suite of products, visit us at www.challengeyourtechnology.com. Or call 866-etrials (387-4257) in the US or in Europe +44 (0) 1795 479041.

www.challengeyourtechnology.com

etrials

SUPERIOR TECHNOLOGY WITH A HUMAN TOUCH

ELECTRONIC DATA CAPTURE
INTERACTIVE VOICE RESPONSE
ELECTRONIC PATIENT DIARIES
WWW.ETRIALS.COM

Dr. Sam **Holtzman**

Risk management refers to a rich set of related methods and techniques. While many see risk management as a way to reduce the probability of undesirable events and mitigate their consequences when they occur, the value of risk management is greatest when it considers both the upside and the downside of management actions and yields robust plans to maximize value.

Jeffrey **Fetterman**

The bottom line is there is absolutely no way to completely eliminate human failures; it is just not a reasonable goal. Instead companies should put in place plans that reduce the incidence of failure without ever expecting that it will be completely eliminated, then build in redundancies or backups that anticipate the failure of one stakeholder and back it up by another stakeholder to mitigate those effects.

If a plan is too complicated, physicians may not use the product and, on the other hand, if it is not rigorous enough, physicians may not feel confident prescribing the product. An optimal RiskMAP addresses factors that balance this equation.

Mr. Fetterman says this requires that pharmaceutical companies provide physicians with appropriate tools and procedures and information that helps them to use the product safely and effectively, build healthcare provider confidence, and make patients comfortable with following appropriate procedures.

Mr. Guselli agrees that the risk-management programs accompanying drugs that come to market are going to have to find the right balance of tools and interventions to be truly successful.

"If the product's program is not thorough enough to really manage risk, a possible adverse event can occur with consequences ranging from patient harm to market withdrawal and bad press for the company," he says. "If a program is too risk management heavy, it becomes a barrier to access for the patient and use by the physician. The market potential of a drug could be affected."

In other industries, companies can remove a product from the market to completely eliminate or greatly reduce risk, but removing a medical treatment from the market could potentially hurt those patients who derive therapeutic benefit.

"Eliminating access to a product is sometimes an effective way to mitigate risk, but for the pharmaceutical industry, that may not actually lower the total public health risk because the underlying risk of the condition still remains," Mr. Fetterman says.

barriers and obstacles

One big challenge for the industry lies in coordinating risk-management initiatives throughout the enterprise. To effectively analyze all the areas of risk, whether it be companywide, portfolio level, or product specific, a clear plan formulated in an organized manner is key and by far the industry's biggest challenge, according to Mr. Frank.

"The biggest problem is that most companies have to get organized and understand all of the compliance mandates, as well as all of the risks that exist within the organization," he says. "Management needs to understand and be able to group the constituencies that are impacted by these different processes. Whether it is an R&D process or a code of conduct, risk management is about awareness and control procedures, many of which are imbedded with other business processes. Without an organized plan of attack and a risk-aware organization, controls will get lost in the heat of battle and performance will suffer."

Solutions that cross organization silos are difficult to come by, and pharmaceutical industry experts say risk-management programs will be no different.

"Risk management is going to face the same challenges as any program that is implemented across the organization, and maybe even more so because the line between development and marketing is going to get stepped on pretty hard when it comes to risk management," Mr. Guselli says. "That is a very significant challenge in terms of the competencies, skills sets, attitudes, and perceptions of this particular exercise in the pharma industry."

Another challenge to enterprisewide programs is making them general so they apply to many situations, while balancing the unique needs of each product situation.

"Different clinical situations and different risk profiles will require customized approaches to maximize program impact," says Linda Sadler, executive VP and managing director at Adient. "Companies will need to balance the need for broad-scope policies with the need for flexible, adaptable programs."

Creating risk-management processes that address the different issues across a company is difficult and requires the cooperation of many departments.

"Risk management is a very rapidly evolving process, but the challenge for Merck is ensuring a consistent process companywide," Dr. Mulholland says. "This cannot be done in silos; it has to be very transparent and include many different cross-functional departments. Many functional areas will need to cooperate, and that may be one of the obstacles."

Aligning the objectives of the different groups involved in a particular risk-management situation is one of the first steps to overcoming the obstacles.

"For example, when implementing an enterprisewide risk-management plan to manage drug safety, the No. 1 task is to align the objectives of the different groups involved, which typically have very different objectives," Mr. Fetterman says. "The objective of regulatory may be to expedite approval of a product, whereas the objective of medical is to do whatever is necessary to ensure patient safety. The objective of marketing may be to preserve the market viability of the product. These parties think their objectives are mutually exclusive, but if a disciplined process is used when working with those cross-functional groups, a company can actually develop a strategy for RiskMAP development whereby those three objectives can be achieved simultaneously."

Senior management can play an important role in unifying the company behind risk-management strategies and fostering an environment conducive to risk-management practice, according to Ms. Nolan.

"To successfully implement an enterprisewide risk-management plan, there needs to be active and demonstrable commitment from senior management, including the assignment of responsibility and accountability for the risk-management plan," Ms. Nolan says. "Communications need to be planned and executed in a way that highlights the FDA's support for industry taking a justified and documented risk-based approach, that explains the value of focusing on both business and regulatory risks, and that reinforces the need to ensure patient safety, product quality, and data integrity. Furthermore, the risk-management plan needs to be flexible and scalable to reflect the risk profile of each of the organizations and locations within the enterprise."

A commitment from senior management is critical because staff must be motivated to identify risks, particularly in their own projects.

"Predictive risk management can greatly reduce Phase III failures, which are really expensive and visible," Dr. Holtzman says. "But there are strong incentives not to allow any systematic approach to guide decisions because, in the current system, the very decisions that can greatly benefit the company can adversely affect individuals' careers."

This fear may contribute to the negative stigma within a company surrounding the term risk management.

"When the term risk management is used some people get very upset because of the perception that such a plan can be a huge barrier to getting a drug to market," Dr. Morris says. "A real barrier to risk management is internal acceptance. People need to realize that with a plan in place, they can market a drug."

Education also presents another barrier to successful risk management.

"Many in the industry are unfamiliar with pharmacoepidemiology as it relates to risk management," Dr. Lilienfeld says. "An additional challenge is the perceived negative impact of having a risk-management program mandated by the FDA in order to launch a product. Both challenges represent opportunities for professional organizations, such as the International Society for Pharmacoepidemiology, to educate those in the industry about the opportunities provided by such programs."

the risks of the real world

Many of the challenges and obstacles for pharmaceutical companies occur when a drug is used in real-world settings.

"Rare adverse events often are not seen in the clinical-trial program for several reasons," Dr. Reynolds says. "There may not have been enough patients involved in the trial to see one case. And if one case is observed, it is difficult to determine whether that single case represents an increased risk."

Because clinical trials typically aren't conducted in high-risk populations, such as those with increased risk of renal problems, pregnant women, children, and patients with concomitant diseases, the safety issues observed in clinical trials will not be exactly the same as those observed when the drug is introduced for use to the general public.

"Clinical-trial populations are specifically identified and enrolled per a specified protocol for clinical trials, but in the real world there are more complex patients who have failed many drug treatments, have more severe illness, and present a variety of concomitant diseases, and these factors significantly increase the risk of safety issues," Dr. Reynolds says. "So it is tough to get a real handle on risk management and risk assessment until the drug is launched."

Dr. Reynolds suggests the best risk-management practice a company can employ before launch is to look at the clinical-trials data and comparator drugs and really understand the disease that is being treated to best be able to estimate and identify what the risks might be for the new drug.

Challenge the Way You Think About Electronic Clinical Trials

www.etrials.com

Leave Paper Behind

etrials is the only eClinical company with its own EDC, IVR and eDiary technologies —all of which integrate effortlessly with the SAS Drug Development Platform for regulatory compliance and analysis. So if you are looking for a way to make clinical trials more efficient, choose etrials. For more info, visit www.etrials.com. Or call us in the US at 866-etrials or in Europe +44 (0) 1795 479041.

etrials

SUPERIOR TECHNOLOGY WITH A HUMAN TOUCH.

www.challengeyourdata.com
www.challengeyourcro.com
www.challengeyourtechnology.com

real-world benefits

Experts believe that conditioning the marketplace for acceptance of any drug with any risk profile provides a company with an important entryway to the marketplace.

"The drugs that potentially have the most risk associated with them will benefit the most from a risk-management strategy," Mr. Guselli says. "If a company that is in a periapproval phase with a risk-management program begins to provide that training and education to physicians so that they gain confidence in the drug's effectiveness and understand how to use it safely and develop the interest of the thought leaders — this can give a drug an enormous head start. By the time it gets approval from the FDA, the company will have a solid foothold in the marketplace already."

Experts say RiskMAPs can reduce costs associated with negative outcomes and increase prescriber confidence and patient outcomes.

"By integrating the RiskMAP into the core activities for the brand, messages can be delivered most effectively, reducing the need for dual communication streams," Ms. Sadler says. "Taking a proactive leadership role will strengthen the image of the manufacturer and the brand."

According to Dr. Faich, for a product with recognized risks, a risk-management program can result in the ultimate ROI.

"The plan may allow for marketing of an otherwise not marketable product and can maintain the product in the marketplace," Dr. Faich says.

Mr. Fetterman notes that the requirement to develop a RiskMAP can add a major uncertainty in the late-development phases and the lack of a disciplined approach to developing RiskMAPs can result in unnecessary variation that leads to unnecessary costs.

"If there is a replicable process to develop RiskMAPs, a company might be able to eliminate delays in development, which is a significant cost avoidance," he says. "Ultimately, an effective RiskMAP may avoid unnecessary product withdrawal and regulatory delays, which are obviously cost avoidances as well."

The ultimate goal for risk management in the pharmaceutical industry, whether it be a RiskMAP or a risk-management plan for quality in manufacturing, is to improve the condition of a patient with safe, efficacious drugs.

"If properly implemented, a risk-management plan will allow those consumers at an acceptably low risk of serious adverse events to make use of the product while minimizing exposure among those at unacceptably high risk," Dr. Lilienfeld says.❖

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

GERALD FAICH, M.D., MPH. Chief Medical Officer, BBCI, a UBC company, Kansas City, Mo.; BBCI is an international provider of Phase II-IV clinical development services to the pharmaceutical, biotech, generic, and drug-delivery industries. Dr. Faich was formerly head of the Office of Epidemiology and Biostatistics at the FDA. For more information, visit bbclinical.com.

JEFFREY E. FETTERMAN. President and CEO, ParagonRx, Wilmington, Del.; ParagonRx supports the commercialization and growth of pharmaceutical brands by improving the process by which clinicians use them; this process is the key element of effective medical-education and risk minimization-action plans (RiskMAPs). Mr. Fetterman also is coauthor of "A Framework For Pharmaceutical Risk Management." For more information, visit paragonrx.com.

THEODORE W. FRANK. CEO, Axentis Inc., Warrensville Heights, Ohio; Axentis is a leading provider of governance, risk, and compliance management software. For more information, visit axentis.com.

GENE GUSELLI. Cofounder, President, and CEO, InfoMedics Inc., Woburn, Mass.; InfoMedics develops and implements large-scale risk-management systems that communicate the facts about a medication's risks while preserving its benefits; through technologies that optimize safe use of a medication both before and after it is in the patient's hands, manufacturers are able to deliver targeted educational and behavioral interventions, employ distribution controls and systematically measure the impact of risk-management efforts. For more information, visit infomedics.com.

SAM HOLTZMAN, PH.D. Chairman, President, and CEO, Rosa Pharmaceuticals Inc., Cupertino, Calif.; Rosa Pharmaceuticals develops drugs through their critical and highly uncertain proof-of-concept stage; Rosa Consulting is a division of Rosa Pharmaceuticals that provides strategic risk-management and drug-development services to pharmaceutical and biotechnology firms. For more information, visit rosapharma.com.

DAVID E. LILIENFELD, M.D. Senior Director of Drug Safety, InterMune, Brisbane, Calif.; InterMune is a biopharmaceutical company focused on the applied research, development, and marketing of life-saving therapies for pulmonary and hepatic diseases. For more information, visit intermune.com.

LOUIS A. MORRIS, PH.D. President, Louis A. Morris & Associates Inc., Dix Hills, N.Y.; Louis A. Morris specializes in regulatory research and consulting. Dr. Morris spent 23 years at the FDA and is a member of the FDA's Drug Safety and Risk Management Advisory Committee. For more information, e-mail lmorris@optonline.net.

LEYNA MULHOLLAND, PH.D. Senior Manager, Pharmaceutical Development, Merck & Co., Whitehouse Station, N.J.; Merck is a global research-driven pharmaceutical products company. For more information, visit merck.com.

FRANCES E. NOLAN. VP, Consultant, Taratec, Bridgewater, N.J.; Taratec provides regulatory guidance and solutions for the business and information technology challenges unique to the life-sciences industry. For more information, visit taratec.com.

MATTHEW REYNOLDS, PH.D. Senior Director, Risk Management and Safety, MetaWorks Inc., Medford, Mass.; MetaWorks is a healthcare consulting company focused on clinical drug development and commercialization within the pharmaceutical, biotechnology, and healthcare industries. For more information, visit metaworksinc.com.

LINDA SADLER. Executive VP, Managing Director, Adient, Wayne, N.J.; Adient, a CommonHealth company, is a leader in the next generation of full-service healthcare-communications firms. For more information, visit commonhealth.com.