BY DENISE MYSHKO

a New Era of DRUG SAFETY

NEW REGULATIONS IN THE UNITED STATES AND EUROPE **HAVE TRIGGERED A NEED FOR BETTER TOOLS FOR THE COLLECTING, REPORTING, AND ANALYSIS OF PATIENT SAFETY DATA.**

As regulators around the globe demand more data on each drug's profile, the need for technologies to support drug safety has become more pressing. This will require companies to invest in more advanced pharmacovigilance technologies and to develop new processes for the analysis of adverse events both in the postmarketing environment and during development.

A component of the Food and Drug Administration Amendments Act (FDAAA) of September 2007 requires sponsors of drug and biological products that are subject to the risk evaluation and mitigation strategies to submit a proposed REMS. This is a way to manage a known or potential serious risk associated with a drug or biological product. This is an expansion of the RiskMAPs the agency had previously required.

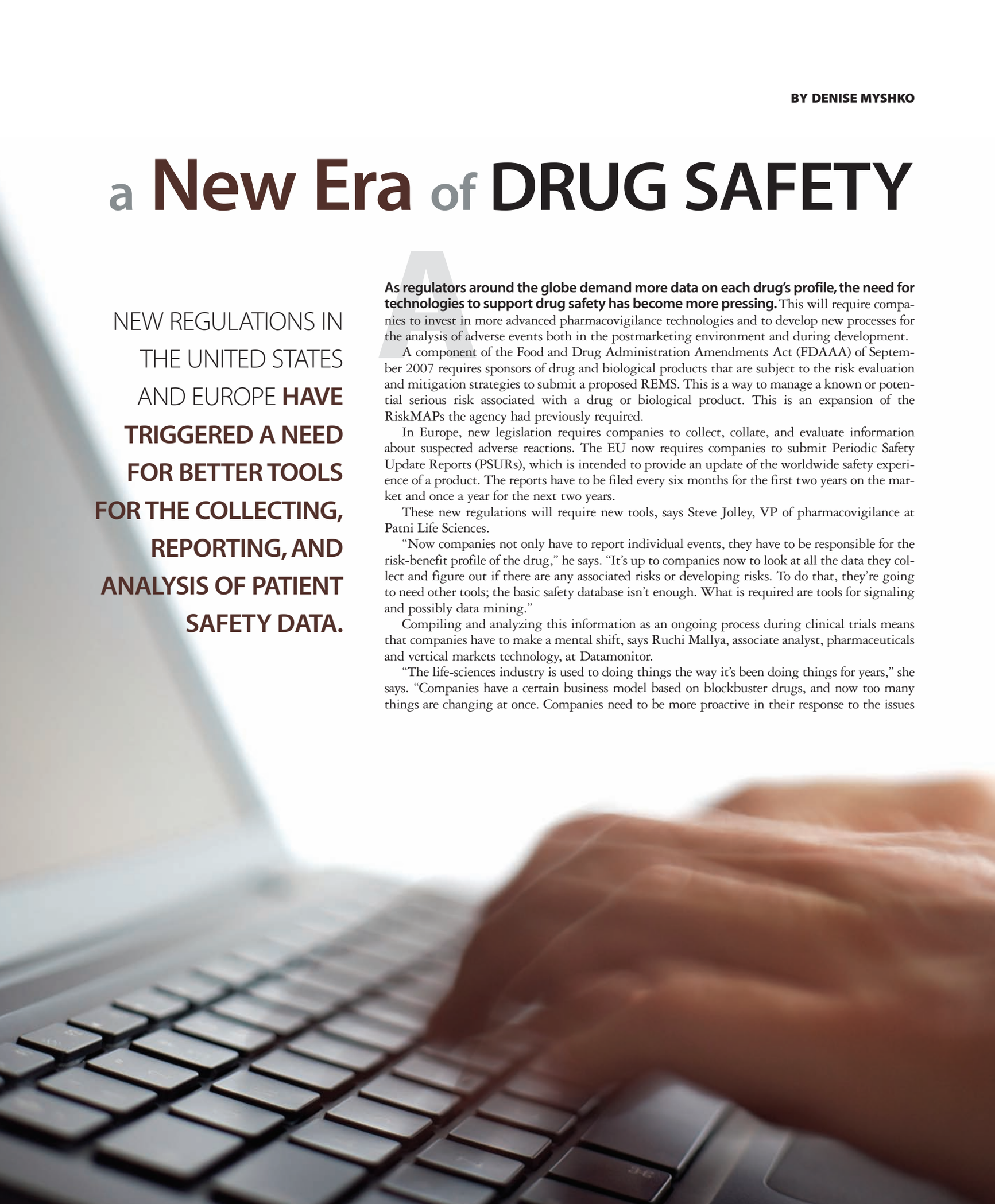
In Europe, new legislation requires companies to collect, collate, and evaluate information about suspected adverse reactions. The EU now requires companies to submit Periodic Safety Update Reports (PSURs), which is intended to provide an update of the worldwide safety experience of a product. The reports have to be filed every six months for the first two years on the market and once a year for the next two years.

These new regulations will require new tools, says Steve Jolley, VP of pharmacovigilance at Patni Life Sciences.

"Now companies not only have to report individual events, they have to be responsible for the risk-benefit profile of the drug," he says. "It's up to companies now to look at all the data they collect and figure out if there are any associated risks or developing risks. To do that, they're going to need other tools; the basic safety database isn't enough. What is required are tools for signaling and possibly data mining."

Compiling and analyzing this information as an ongoing process during clinical trials means that companies have to make a mental shift, says Ruchi Mallya, associate analyst, pharmaceuticals and vertical markets technology, at Datamonitor.

"The life-sciences industry is used to doing things the way it's been doing things for years," she says. "Companies have a certain business model based on blockbuster drugs, and now too many things are changing at once. Companies need to be more proactive in their response to the issues



BRUCE PALSULICH RELSYS INTERNATIONAL

COMPANIES HAVE TO FOCUS ON THE BUSINESS PROCESS AND DECIDE HOW THEY WANT TO FUNCTION GLOBALLY, AND THEN LOOK FOR THE TOOLS THAT WILL FIT INTO THAT MODEL AND HELP THEM MANAGE THE PROCESS.

AMY CAMPBELL SIPERIAN

TO GET THE FULL EFFECTIVENESS OF ANALYTICAL TOOLS, IT'S IMPORTANT TO RECONCILE THE DATA FIRST. IT'S IMPORTANT TO HAVE CONTEXT AROUND THE DATA AND BE ABLE TO LINK AN ADVERSE EVENT TO A SPECIFIC DRUG IN A SPECIFIC TRIAL.

and their processes of determining whether a drug is safe or not. They need to be more transparent about safety issues. This will build a trusting relationship with the end user."

The FDA and the pharmaceutical industry are both in a difficult position, says Kris Joshi, Ph.D., senior director, strategy and business development, at Oracle Health Sciences.

"Patients and consumers want drugs to reach the market faster and more cheaply, but they also want them to be safer," he says. "There is a lot of uncertainty in the marketplace in terms of the pharmaceutical companies' ability to respond to safety concerns while still watching their bottom lines."

Dr. Joshi says a broad-based and dependable safety system will require more than just policing by the FDA.

"What's needed is a neighborhood watch type of approach to safety with hospital, insurance companies, patients, and pharmaceutical companies all playing a role," he says.

For this to happen, Dr. Joshi says, companies have to commit to breaking down silos.

"This might sound obvious, but generally in a development organization, the groups that do modeling and simulation, the groups that track safety, trial operations, and trial design, and the groups that do pharmacokinetic and pharmacogenetic modeling are usually independent silos that tend to use data from one part of the process," he says. "What gets lost is a cross-study focus, which is important for leveraging synergies in terms of scientific understanding and repeatability of certain outcomes across studies. That, in turn, prevents groups from being able to share data and information more easily."

Experts agree that pharmacovigilance requires the accurate collection of data from many sources, including clinical trials, postmarketing, medical practitioners, and consumers. Consistent collection of data and overall integration of those data have to improve, experts say.

"To realize the full effectiveness of analytical tools, it's important to reconcile the data first,"

Sound Bites From The Field

PHARMAVOICE ASKED EXPERTS FROM CONTRACT RESEARCH ORGANIZATIONS WHICH PHARMACOVIGILANCE TECHNOLOGIES HAVE THE MOST PROMISE, AS WELL AS BEST PRACTICES FOR IMPLEMENTING THESE SYSTEMS.

DIPTI AMIN, M.B.B.S., is Senior VP and Global Head, Quintiles Drug Safety and Medical Affairs, Research Triangle Park, N.C., which provides a broad range of professional services in drug development, commercialization, and strategic partnering for the pharmaceutical, biotechnology, and medical-device industries. For more information, visit quintiles.com.

"There is no specific set of tools that holds the most promise. Rather it is the approach: thorough prospective and retrospective data collection and evaluation systems and using up-to-date analytic methodologies grounded in clinical evaluation of the findings.

One should not rely on a single tool but rather a set of tools that include data mining of large data sets from several sources, individual case review and assessment, and finally independent validation of those findings. Once validated, the findings must be communicated in terms that are understandable to each audience: regulators, company officials, the financial community, providers, prescribers, and patients. Independent monitoring and advisory boards can guide the collection, evaluation, and communication of risk-benefit information. Companies should develop a multifaceted evaluation methodology and a strategic communication plan that are continuously evaluated for effectiveness."

ROBERT BADER, PHARM.D., is Director, Product Safety Services, Periapproval Services, at Covance Inc., Princeton, N.J., a comprehensive drug-development services company. For more information, visit covance.com.

"In the postmarketing safety arena, there is no gold standard. Therefore, multiple tools are necessary to address different issues. Confidence in conclusions is greatest when data from multiple sources all point in the same direction. Passive surveillance may still be one of the best tools for detecting signals because of its large and broad patient exposure without restrictions on comorbidities, con-meds, etc., and the inclusion of off-label use data. But this approach cannot be used to determine incidence rates and lacks adequate controls. Registries, REMS programs, and observational studies are typically used to target specific patient populations and help determine the magnitude of the risk as well as any potential risk factors for the event. Large, simple trials are best used to quantify rare events or to address unanticipated safety issues that are identified after approval. Planning of pharmacovigilance activities ideally should be driven by issues identified from pre- and postapproval data and outlined in a safety specification. As detailed in the EU guidelines, a pharmacovigilance and risk management plan should begin early in product development and evolve as new information is collected."

TARA FERGUSON is Director, Pharmacovigilance Operations, Parexel International Corp., Waltham, Mass., a global services organization that provides expertise in integrated clinical development, medical communications, and regulatory affairs, as well as technologies to expedite time-to-market. For more information, visit parexel.com.

"Earlier detection of signals and prompt action on this information should lead to improved patient safety. A system where automatic intelligent signal detection allows for immediate notification of required updates to a product's label based on changes to an adverse event profile sounds highly useful, but a large time and cost investment could be involved in developing and testing such a system. It is imperative, however, that companies think about technologies to support pharmacovigilance not as a luxury but rather a necessity. The right system should be global too, flexible for differing requirements, and adaptable to change with evolving regulations."

KRIS GUSTAFSON is Senior VP, Interactive Technologies & Lifecycle Sciences, Icon Clinical Research, North Wales, Pa., a global provider of outsourced development services to the pharmaceutical, biotechnology, and medical-device industries. For more information, visit iconplc.

"The adoption of advanced pharmacovigilance tools will be critical as the regulations surrounding drug safety increase. Specifically, adverse event reporting, signal detection, and data management and data mining tools will be important to handle the vast amounts of safety data. The ability to perform real-time, ad-hoc analysis in a clinical trial will require improved signal detection and data mining tools. Data mining is frequently used in postapproval surveillance. The use of data mining in the clinical-trial process is less common. Early signal detection will allow companies to recognize safety issues more quickly, preventing unneeded suffering.

The best practices for using pharmacovigilance technologies are similar to the same best practices that should be used for implementing any tool, which is to fully understand the three critical components: the people, the process, and the technology."

KEN HINTZE, PH.D., is VP, Global Clinical Safety and Pharmacovigilance, at Kendle, Cincinnati, a global clinical research organization providing a full range of early- to late-stage clinical development services for the world's biopharmaceutical industry. For more information, visit kendle.com.

"One way to confirm (or refute) a potential increased risk of an adverse event is to undertake observational or

says Amy Campbell, senior manager, field solutions, at Siperian. "It's important to provide context around the data. For example, being able to connect an adverse event to a specific drug, to a trial, and then to a specific trial subject provides the context in which to figure out whether there are trends related to an adverse event that people need to be alerted to."

specific clinical endpoint driven studies. The introduction of Web-based technologies has revolutionized the collection of all clinical data and safety data in particular. The Internet, when coupled with an electronic adjudication system, makes it possible to give experts instant remote access to morbidity/mortality information. Completion of an electronic adjudication form by experts from any location in the world gives those undertaking the study immediate access to the outcome data. Faster adjudication should make it easier to update the benefit-risk ratio, particularly when questions are being asked about a product's side-effect profile."

SAMEER THAPAR, PHARM.D., is Director, Global Safety Surveillance and Pharmacovigilance, Omnicare Clinical Research, King of Prussia, Pa., a Phase I to IV contract research organization serving the biopharmaceutical and medical-device industries. For more information, visit omnicarecr.com.

"Until now, signal detection and evaluation have operated on a variety of algorithms, none structured to produce the most timely and valuable risk-management solution. Companies have employed a variety of roles to bridge these deficiencies, such as risk-management and assessment personnel, safety trending personnel, and epidemiological personnel. But even with the amalgamation of all these entities, no one can accurately predict a model for patient safety in a compound or series of clinical studies. Newer, Internet-based software solutions are on the rise with a goal to harness the global knowledge and funnel this into meaningful safety data.

A best practice for pharmacovigilance lies with accepting technology at its first awareness. For instance, new media technology such as RSS feeds and forums offer a wealth of communication tools as well as gathering areas for adverse event data mining. It is with some risk that these technologies are implemented, but with proper awareness and procedures for handling data within the company, these technologies can benefit the safety professional by making the signal stronger and more relevant."

◀ **NAGARAJA SRIVATSAN** COGNIZANT

THE TOOLS AND TECHNOLOGY OFFER A LOT OF POTENTIAL BUT HOW YOU HARNESS THEM IS KEY IN MAKING DATA ANALYTICS AND DATA MINING SUCCESSFUL.

Pfizer's current system of spontaneous reporting has many paper-based aspects to it, says Michael Ibara, Pharm.D., head of pharmacovigilance information management at Pfizer.

"If doctors want to report adverse events to the FDA now, they can go online to find the form to fill out, but the online form is basically an image of a paper form," he says.

Pfizer is working with CRIX International, Partners HealthCare/Brigham and Women's Hospital, and the FDA on a project, called ASTER, to streamline one part of pharmacovigilance: spontaneous reporting of adverse events. CRIX, the Clinical Research Information exchange, is developing a system that would allow physicians to report adverse events using data from the patient's electronic health record. (For more information about ASTER, see box on page 26.)

NEWER TECHNOLOGIES

Current tools on the market do a good job of capturing the data entry from various sources of adverse events and providing the analysis and reporting framework to regulatory authorities, say experts at Oracle Health Sciences.

But going forward, they contend, the industry needs to be more proactive and identify signals related to an adverse event earlier.

An informal survey early this year by Relsys International found that that slightly more than 50% of companies already have a signal management methodology in place or are defining it, and the remaining companies plan to do so within the next year or so.

"The environment is becoming much more competitive and the information that is available to the public in terms of the benefit/risk profile is certainly part of the landscape in terms of whether a drug is approved," says Bruce Palsulich, chief innovation and strategy officer at Relsys. "Companies have to have tools in place to avoid being surprised when regulators say they've identified a potential signal."

▲ **RUCHI MALLYA** DATAMONITOR

THERE IS A LOT OF ANALYSIS DONE DURING TRIALS BUT TOOLS, SUCH AS SIGNAL DETECTION SOLUTIONS, ARE NOT BEING USED TO DO A FULL-BLOWN ANALYSIS OF SAFETY IN CLINICAL TRIALS.

Mr. Jolley says new tools aim to help tease out relationships within the data.

"With the right tools it is possible to get the information into one coherent data set, apply some analyses, and visualize trends," he says. "From there, it is possible to drill down and find out what's really happening. Then companies can develop hypotheses about what is going on and what the potential signal could be."

Experts agree signal detection tools hold promise, although there are some challenges.

"Signal detection is an emerging area," Dr. Joshi says. "There are many different algorithms needed to detect an early sign or signal related to a safety issue. The problem is that the process is based on numbers or metrics rather than on science or clinical data."

Another challenge, he says, is that there are no standards for signal detection.

"There is no standard agreement of what an early signal is," Dr. Joshi says. "This is a prob-

DR. KRIS JOSHI ORACLE HEALTH SCIENCES

COMPANIES ARE STARTING TO RECOGNIZE THE VALUE OF PRESERVING THE INTEGRITY OF THE KNOWLEDGE BASE COMING FROM DISCOVERY AND MAKING THE DATA AVAILABLE TO THE DEVELOPMENT SIDE; THESE DATA THEN CAN BE USED TO DEVELOP AN EARLY UNDERSTANDING OF THE SCIENTIFIC IMPLICATIONS OF ANY ADVERSE EVENTS.

lem because the FDA, healthcare providers, and pharmaceutical companies all need to have a common understanding and agreement of what an early signal is and then each associated stakeholder can take the appropriate action. It's in no one's best interest to take a drug off the market if it is actually showing great benefit for certain people."

Mr. Palsulich says many of the signal detection systems are bolt-on components that aren't necessarily well-integrated into the overall process or work flow.

"Having integrated online reporting and analytical tools is a benefit to managing signal detection as an overall process instead of just identifying statistical anomalies," he says.

Annette Stemhagen, Dr.PH., VP, epidemiology and risk management, at United BioSource says another challenge to overcome is the number of false positives that could come from mining databases for safety signals.

"Data mining is in the early stages and using it properly is a challenge," she says. "False-positive signals take a lot of effort to investigate to determine whether they are true signals or false signals. We're still working through the techniques and combination of techniques."

With regard to the databases themselves, Dr. Stemhagen says companies have to make sure they are working with and are managed by someone who is an expert in those databases.

"These databases are not created for research; they are created for the most part for billing purposes," she says. "It's important to understand how the data go in before correctly taking the data out. People can go very

A DIFFERENT MODEL FOR SPONTANEOUS REPORTING

A new model is beginning to emerge for the reporting and collection of adverse event data. Healthcare providers, health plans, and pharmaceutical companies are teaming up to use electronic health records to populate forms for submission to the Food and Drug Administration.

One such project is ASTER, which is a collaboration between Pfizer, CRIX International, Partners HealthCare/Brigham and Women's Hospital, and the FDA. Under the agreement, CRIX, the Clinical Research Information exchange, is developing a system that would allow Partners' physicians to report adverse events using data from a patient's electronic health record. Physicians would see a single-page electronic form, which uses CDISC standards, that has been prepopulated using data from the patient's record.

A three-month pilot is expected to begin by the end of this year with a small group of physicians in ambulatory practice at Partners HealthCare, an integrated healthcare system that was founded in 1994 by Brigham and Women's Hospital and Massachusetts General Hospital.

For the physician, filling out the forms for report adverse events is time-consuming, says Michael Ibara, Pharm.D., head of pharmacovigilance information management at Pfizer.

"Estimates of how long it takes a physician to fill out the form range from 20 to 40 minutes," Dr. Ibara says. "The current system of spontaneous reporting is paper based, and the online form is basically an image of the paper form. Often, when a doctor realizes a patient has an adverse event, he or she doesn't have the form on hand. Or when they take the time to fill out the information they don't have patient's record on hand."

Dr. Ibara says the ASTER project aims to take the information already available in health plans' systems to make the reporting faster and easier for physicians.

"We can download information directly to a report so the doctor only has to push a button to report an adverse event," he says.

The data then go to CRIX, which prepares the information according to the current reporting standards and sends the report to the FDA.

"This move away from paper means that a report that may have taken up to 15 days to get to the FDA now gets to regulators in minutes," Dr. Ibara says. "Once this change occurs, a new business model will be in place for spontaneous reporting. There will be many different ways of looking at the information. And it affords neutral third parties, such as CRIX, a role in standardizing that information."

All stakeholders will need to work to together to reach this common goal.

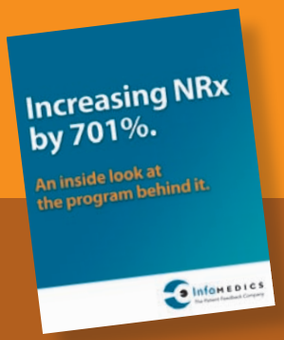
"This is a true collaboration between those delivering healthcare, the people responsible for drug safety, and regulators," Dr. Ibara says. "This is a rare collaboration, and in my opinion one that is very much needed going forward."

See us at EyeForPharma
Patient Adherence
and Persistence Summit
October 23-24, 2008
Hyatt Harborside, Boston
Booth #21

4:1

The average ROI for pharma brands using patient-feedback programs from InfoMedics.

If you like that number, you'll love these: An average increase in NRx of 100.2% among physicians with patients. A vote of confidence from 88% of doctors who say they value this kind of patient feedback. And an impressive 15 out of 15 top pharmaceutical companies that turn to us, year after year. The reason? Only InfoMedics knows how to run patient-feedback programs that can lift NRx and TRx to jaw-dropping levels.



Get the exclusive case study:

Ready to create your own results worth bragging about? **Learn more at www.infomedics.com/NRx or call 1-888-452-9697.**

InfoMEDICS
The Patient Feedback Company

Visit www.infomedics.com/NRx today.

wrong if they are not familiar with all of the nuances of the data."

Nagaraja Srivatsan, VP, head of North America, Life Sciences, at Cognizant, says the evolution of safety systems is progressing in the same way as electronic data capture systems.

"A few years ago, automating the process and streamlining and capturing all of the safety and adverse event data in an electronic form was a challenge," he says. "Now that is par for the course, and people are looking at how to build upon this type of automation. Now that the information has been captured, the next step is to get better insights from these data. You need the ability to apply signal detection techniques on these data."

There is also a need for changing pharmacovigilance processes, Mr. Srivatsan says.

"As with any software solution, these tools are simply a method by which activities are conducted," he says. "Not having the right business processes in place before implementing one of these technologies will lead to suboptimal use of the technologies. They are all very rich tools and they can do an awful lot of things, but each pharma company has a different priority and has different challenges."

Mr. Srivatsan adds that signal detection is an art and not a science and that systems have to be able to handle all aspects of global drug safety operations.

"On the one hand, the system has to be able to look at global information to identify signals while being responsive to health authorities in different continents and in some cases different countries with different reporting regulations," he says. "Flexibility to those individual authorities is the key right now."

DEVELOPMENT ISSUES

So far the industry has focused more on reporting and using high-tech statistical tools for adverse events in the postmarket arena. But emerging regulations could just change that.

The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, nonprofit organization that makes recommendations to the International Conference on Harmonisation (ICH).

The CIOMS VII Working Group is proposing an internationally harmonized document, the Development Safety Update Report (DSUR), which is modeled after the Periodic Safety Update Report (PSUR) for marketed products. This would apply the techniques that are used in the postmarketing world to analyze the safety of prescription drugs in the clinical area.

According to a Datamonitor report, the use of data mining and signal detection in clinical trials is a relatively new concept. Using advanced signal detection technologies throughout the clinical-trial process would allow researchers to perform ad hoc, close to real-time analysis on the data, reducing time in the back-and-forth interchange between researchers and statisticians.

"There is a lot of analysis done during clinical trials, but what hasn't happened is the use of standing data to do a full-blown analysis of safety during the trial," Ms. Mallya says. "With the amount of data available to companies from trials, it is possible for companies to conduct the same type of safety analysis they've done for postmarketing studies. The tools available now can be applied to clinical research for the most part; adjustments will need to be made because of the nuances with the different trial phases."

Dr. Joshi says companies are starting to categorize and mine the insights that are coming out of the research in the discovery and the development phases of R&D.

"Before discovery data stayed in discovery and the development data stayed in development," he says. "Now companies are starting to recognize the value of preserving the integrity of the knowledge base coming from the discovery side and making these data available to the development side."

He says this requires a tremendous amount of integration, which for the most part is lacking in the R&D environment.

"Integration is required at the outset between the major streams of evidence — data from EDC, safety data from adverse events, and operation data related to the trial, so the study can be modified and steered in a different direction if needed," Dr. Joshi says. ✦

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

Experts on this topic

AMY CAMPBELL. Senior Manager, Field Solutions, Siperian Inc., Foster City, Calif.; Siperian, a provider of a flexible master data management platform, helps companies unify their critical data about customers, products, and organizations. For more information, visit siperian.com.

MICHAEL IBARA, PHARM.D. Head of Pharmacovigilance Information Management, Pfizer Inc., New York; Pfizer is a research-based biomedical and pharmaceutical company. For more information, visit pfizer.com.

STEVE JOLLEY. VP, Pharmacovigilance, Patni Life Sciences, Bridgewater, N.J.; Patni Life Sciences is a consultancy that provides regulatory compliance and system life-cycle services to address the unique business and information technology challenges faced by life-sciences companies. For more information, visit patni.com.

KRIS JOSHI, PH.D. Senior Director, Strategy and Business Development, Oracle Health Sciences, Oracle Corp., Redwood Shores, Calif.; Oracle is an enterprise software company. For more information, visit oracle.com.

RUCHI MALLYA. Associate Analyst, Pharmaceuticals & Vertical Markets Technology, Datamonitor, New York; Datamonitor provides online data, analytic, and forecasting platforms for key vertical sectors. For more information, visit datamonitor.com.

BRUCE PALSULICH. Chief Innovation and Strategy Officer, Relsys International Inc., Irvine, Calif.; Relsys International provides system solutions for drug safety, pharmacovigilance, and risk management. For more information, visit relsys.net.

NAGARAJA SRIVATSAN. VP, Head of North America, Life Sciences, Cognizant, Teaneck, N.J.; Cognizant is a provider of information technology, consulting, and business process outsourcing services. For more information, visit cognizant.com.

ANNETTE STEMHAGEN, DR.PH. VP, Epidemiology and Risk Management, United BioSource Corp., Bethesda, Md.; UBC is a global pharmaceutical services organization that helps emerging and established life-sciences companies develop and commercialize medical products. For more information, visit unitedbiosource.com.