Unlocking the power of pharmacovigilance*
An adaptive approach to an evolving drug safety environment

PricewaterhouseCoopers' Health Research Institute

*connectedthinking

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Executive summary

The idea that controlled clinical trials can establish product safety and effectiveness is a core principle of the pharmaceutical industry. Neither the clinical trials process nor the approval procedures of the U.S. Food and Drug Administration (FDA), however, can provide a perfect guarantee of safety for all potential consumers under all circumstances. Despite this fact, there are viable solutions that pharmaceutical companies can implement to support pharmacovigilance—the systematic detection, assessment, understanding and prevention of adverse drug reactions. When built into existing research and development practices, pharmacovigilance activities can enhance patient safety while reducing or even preventing costly safety-related withdrawals.

Currently, however, pharmaceutical executives face a number of challenges in the area of pharmacovigilance. In the four decades from the thalidomide tragedy to the recent concerns about Vioxx, companies have used pharmacovigilance methods designed to identify rare, easily identified safety problems At the same time, we have seen the growth of a fragmented healthcare system that has lacked a unifying infrastructure. As a result, this system operates primarily in reaction to rather than in anticipation of major pharmaceutical safety events. As drug consumption has increased and the public has grown to expect greater drug safety, the traditional reactive approach has proven largely incapable of addressing shifts in public expectations and regulatory and media scrutiny. This reality has revealed issues in the four areas involved in patient safety operations: organizational alignment, operations management, data management, and risk management.

When appropriately aligned and supported, these areas can work together to enable a flexible, adaptable, and proactive system for addressing patient safety issues. Companies can unlock the power of their pharmacovigilance activities by creating an operational framework that supports the key patient safety infrastructures. The following are recommendations for companies developing an adaptive pharmacovigilance framework:

1. Align and clarify roles, responsibilities, and communications
- Develop an objective, data-driven, team-based approach to risk monitoring and evaluation
- Implement well-defined decision-making models, escalation processes, and communication channels
- Determine the pharmacovigilance workload and sufficiently resource the required effort
- Designate a pharmacovigilance operating model and business process owner
- Ensure that appropriate process and organizational checks and balances are in place to limit bias and manage regulatory risk

2. Standardize pharmacovigilance processes and data management
- Align operational activities across departments and across sites
- Implement process-driven standard operating procedures, work instructions, and training materials
- Integrate safety data through data and system interoperability standards
- Implement workflow management technology to ensure appropriate transparency and accessibility of safety information
- Select a vendor that best matches the pharmacovigilance operating model, business process and vendor/system selection criteria

3. Implement proactive risk minimization
- Develop risk management action plans based on pre-established risk scoring mitigation processes
- Implement data mining techniques to bolster safety analytics, reporting, and investigation
- Incorporate continuous improvement activities and standardized risk communication plans
- Create a dashboard that summarizes and promotes timely awareness of safety risks across the portfolio and timely execution of safety risk minimization activities

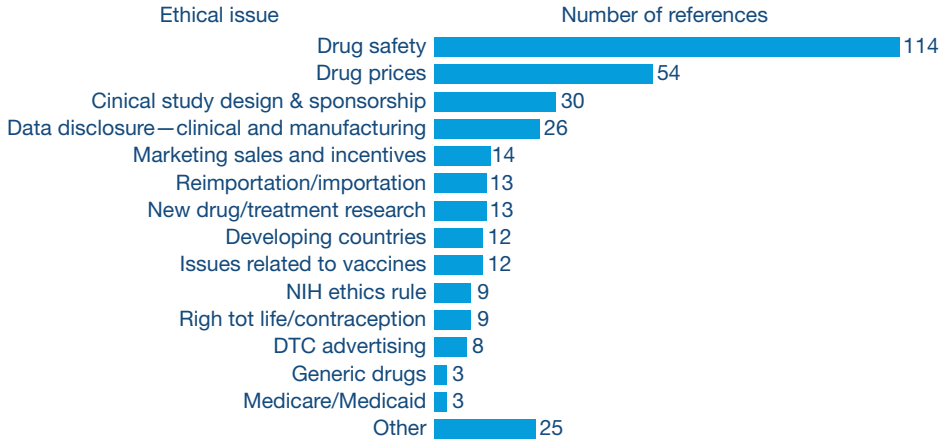
Background

The challenge to the pharmaceutical industry

A chief problem that pharmaceutical companies face in the area of pharmacovigilance is the possibility that a medicine may be taken in a manner for which it was neither intended nor clinically tested. This can happen for a number of reasons: the number of participants in the average clinical trial is dwarfed by the thousands or even millions of biologically unique patients who may take a marketed treatment; medicines can be taken in combination with other therapies with which they have not been clinically tested; and medicines may be prescribed for an indication different from the one for which they were approved. All of these factors, including preexisting conditions, may increase the odds that serious adverse events absent in clinical trials might easily occur postmarket.

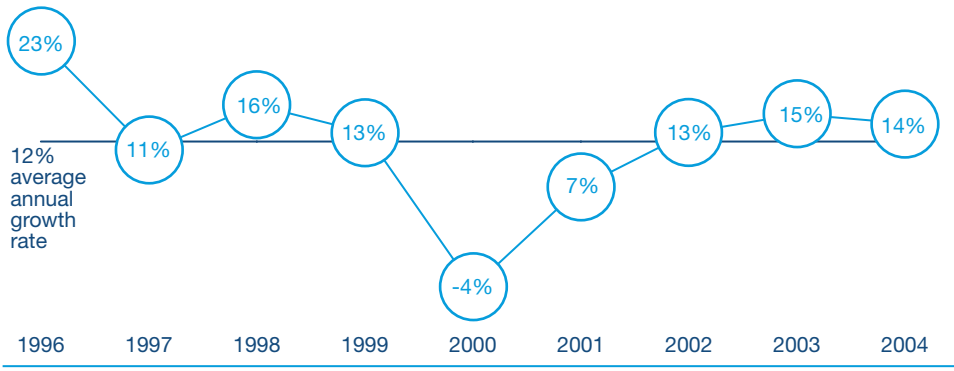
Neither these odds nor the risks they represent are well understood by consumers, the result being that a spate of safety-related product withdrawals has hastened the recent steep decline of public confidence in the ability of pharmaceutical companies and regulators to ensure safety.

Exhibit 1: Frequency analysis of ethical issues



Source: "Front Page Pharma," by Stephen J. Porth and George P. Sillup, Pharmaceutical Executive, February 1, 2006.

Exhibit 2: Prescription drug adverse event report growth, U.S., since 1995



Source: "CDER 2004 Report to the Nation: Improving Public Health Through Human Drugs," Center for Drug Evaluation and Research. August 22, 2005.

Increased media scrutiny

Growing public concern over drug safety also has spurred the media to focus on this issue. Drug safety was the top issue in Pharmaceutical Executive's Annual Media Audit 2005, with drug safety and development issues dominating more than half of the print media coverage (Exhibit 1). Heightened media and public

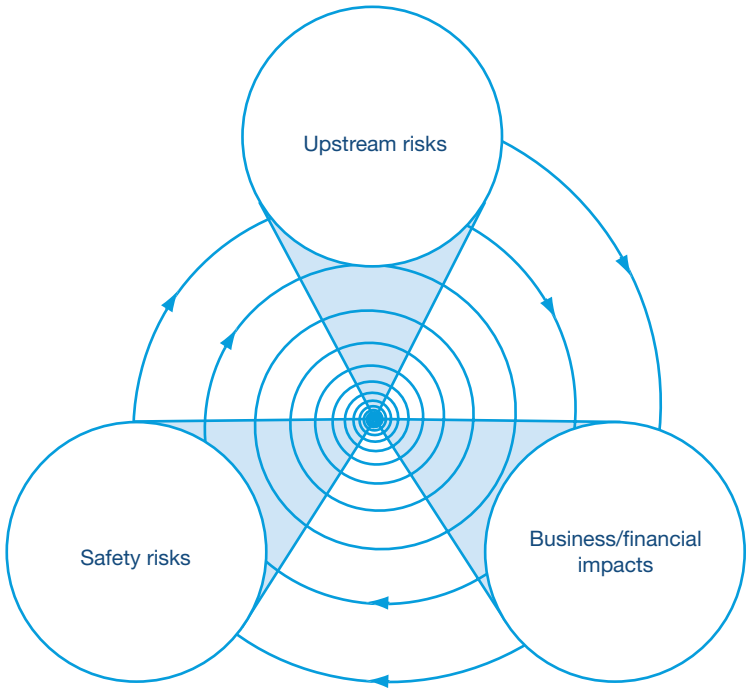
awareness has combined with greater scrutiny by regulators and elected officials to create a rapidly evolving—and potentially dangerous—environment for pharmaceutical companies.

One reason for such media scrutiny is the release of reports from the FDA and the World Health Organization's Vigibase (a global adverse drug reaction database) of significant increases in the number of adverse events reported in recent years. The FDA, for example, shows an average growth rate of 12% annually in adverse event reports to the agency from 1995 through 2004 (Exhibit 2). The causes and implications of the increase are the subjects of much debate. Despite increases in adverse event reports, safety-based drug withdrawals in the U.S. have remained essentially flat, at about 3 per 100 New Chemical Entity approvals for the past 35 years.[1]

The public may view the increase in reported adverse events negatively, but the growing number of reports may result, in part, from increased awareness in the medical community and the sheer increase in drug consumption. The industry could benefit greatly if the public better understood these factors and their impact on pharmacovigilance.

The impacts of safety issues are not limited to perception alone. Safety issues can lead to regulatory fines, litigation costs, reduced market share, diminished brand equity, and decreased shareholder value. Such impacts may affect a company's ability to finance safety initiatives and thereby induce a downward spiral of further safety-related strategic and operational issues (see Exhibit 3).

Exhibit 3: The downward safety spiral



Consumers do not hold industry solely responsible for safety issues but blame government as well. A 2005 consumer survey conducted by the Henry J. Kaiser Family Foundation reported that 77% of respondents were "very" or "somewhat" confident in the ability of the FDA to ensure that prescription drugs are safe. Even so, 22% were "not at all" or "not too" confident in the FDA's oversight ability.[2]

"Unfortunately, the public has been led to believe that FDA's approval of a drug means that FDA's promise of 'safe and effective' is an absolute," said Judith M. Sills, Pharm.D., head of global safety intelligence at Novartis Pharmaceuticals. "Neither the FDA nor the industry has done a good job in educating consumers that these terms are relative and not an absolute guarantee."

And the public's level of confidence is slipping. A more recent Wall Street Journal Online/Harris Interactive Poll paints an even bleaker picture: 58% of respondents said they think the FDA does only a "fair" or "poor" job of ensuring the safety and efficacy of new prescription drugs—up significantly from the 37% who said so just two years ago.[3] To some degree, these opinions are driven by consumers' misunderstanding of the relative nature of the "safe" and "effective" descriptions as they apply to pharmaceutical products.

"The public perception that every problem can be solved by a pill has to change," said Raymond L. Woosley, M.D., Ph.D., president of the Critical Path Institute. "Drugs are foreign chemicals, and while they have beneficial effects, they also have side effects. The public must understand that because of the biologic differences between individuals, all side effects cannot be discovered prior to marketing. Therefore, it is to be expected that drugs will be taken off the market from time to time."

Nearly all medical treatments and products may carry some degree of risk to patient health. The public's ignorance of the risk profiles of prescription drug products can significantly affect its expectations about and reactions to safety events.

Greater regulatory and legislative scrutiny

Scrutiny of the pharmaceutical industry also extends to the regulatory and legislative arenas. Regulators and legislators are subject to public opinion, and this has driven expanded activity in the area of drug safety.

Despite the FDA's establishment of the Drug Safety Oversight Board in 2005 and the consequent drafting of a policy on major postmarket decision making, a March 2006 U.S. Government Accountability Office (GAO) report criticized the FDA for lacking "clear and effective processes for making decisions about, and providing management oversight of, post-market safety issues."[4] In particular, the report noted the FDA's inability to ensure that long-term, postmarket follow-up studies get conducted, noting that only 24% of agreed-upon studies were actually conducted from 1991 to 2003.

Partly in response to the GAO's report, the FDA created the position of associate center director for safety policy and communication within the Center for Drug Evaluation and Research to oversee drug safety issues and policies.[5]

The FDA also recently changed—for the first time in more than 25 years—the requirements for pharmaceutical package inserts and warning labels, released 11 new patient safety guidance documents, and announced plans to release guidance on eight other safety-relevant topics during the remainder of 2006.[6]

The March 2006 GAO report also has inspired Congress to work toward enhancing the oversight authority of regulatory agencies around postmarket drug safety. Although a measure that would have granted the FDA authority to compel drugmakers to conduct postmarket clinical trials failed, similar legislation is in progress, and the Senate Finance Committee has adopted FDA oversight—and specifically, patient safety—as part of its agenda.

The recent steps in the U.S. parallel a heightened focus on patient safety in Europe, both within the European Union and within individual states. This new emphasis on pharmacovigilance, while welcome, does pose challenges to U.S. pharmaceutical companies doing business in Europe.

"Historically, the European authorities adopted a more philosophical view of pharmacovigilance, but now we're seeing them move toward the compliance, surveillance, and qualifying data that the U.S. has typically stressed," said Barry Arnold, former vice president of global patient safety at AstraZeneca. "And the Americans are moving more toward evaluating the quality of systems and not just the number of reports."

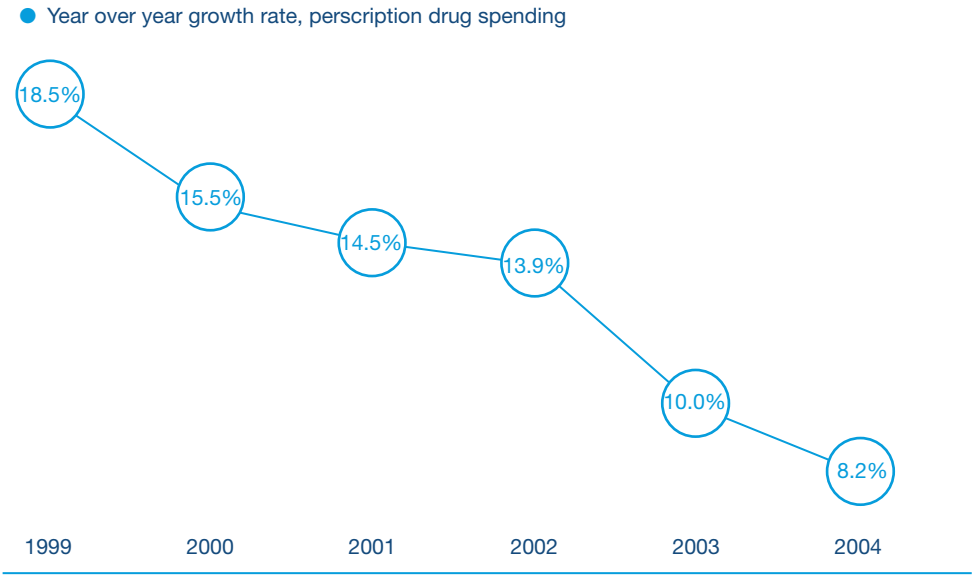
Until the International Conference on Harmonization (ICH) has standardized regulations across the globe, companies will grapple with differing and evolving cross-border rules and safety reporting requirements. "It's become clear that even if a country's regulatory authority signs onto ICH, they'll put their own spin on the regulations. This will continue to be a challenge," said Sills.

Investment in pharmacovigilance

Any discussion of drug safety must acknowledge the fact that there is relative underinvestment in pharmacovigilance. A 2003 study by Duke University and the University of North Carolina at Chapel Hill pegged spending on patient safety monitoring following FDA approval at just 0.3% of sales revenue across the top 20 pharmaceutical manufacturers, even though research and development spending—largely in advance of product approval—consumes 15.6% of revenue at these same manufacturers.[7]

There is no science that dictates that a certain percentage of revenue should be allocated to pharmacovigilance, but—in the face of the potentially huge cost of safety-related withdrawals within the context of heightened stakeholder expectations around drug safety—companies should endeavor to strike a better balance between R&D spending and pharmacovigilance spending. The cost of withdrawals—when viewed against a backdrop of annual drug spending growth, that declined from 18% in 1999 to 8% in 2004 (see Exhibit 4)—demonstrates that companies face a rapidly diminishing margin for safety-related error. And government actuaries recently predicted that drug consumption could continue to decline in the future, making it that much harder to recoup losses due to safety-based withdrawals.[8]

Exhibit 4: The decline in prescription drug spending growth, 1999-2004



Source: *National Health Expenditures, Centers for Medicare & Medicaid Services.*

The clear implication is that companies should invest more now to implement pharmacovigilance measures. The question, then, for firms willing to make this expanded commitment is: How best to deploy that additional time and money? PricewaterhouseCoopers interviewed 34 industry experts on patient safety and pharmacovigilance and consulted thought leaders who have successfully addressed similar challenges in other disciplines both within and beyond the pharmaceutical industry. Their insights provided the basis for the recommendations outlined here.

The reactive nature of pharmacovigilance

The interviews found that pharmacovigilance programs at different companies are at various stages of maturity. Regardless of their degree of pharmacovigilance maturity, however, nearly all of the companies interviewed are working to improve their pharmacovigilance efforts.

"The fact that pharmacovigilance is in the spotlight is a mixed blessing," said Jean-Louis Saillot, M.D., vice president and head of global pharmacovigilance, Schering-Plough. "The increased scrutiny makes the challenges harder to surmount, but that same scrutiny forces us to meet those challenges head-on."

Companies face this challenge because the pharmacovigilance methods developed in the four decades since the thalidomide tragedy have been designed to identify rare, easily identifiable safety problems at the same time as we have seen the growth of a fragmented health-care system that has lacked a unifying infrastructure. As a result, this system operates primarily in reaction to rather than in anticipation of major pharmaceutical safety events.

Unlocking the power of pharmacovigilance

As drug consumption has increased and the public has grown to expect higher levels of drug safety, the traditional reactive approach has proved largely incapable of addressing shifts in public expectations and regulatory and media scrutiny. This reality has revealed issues in the four areas, or infrastructures, involved in patient safety operations: organizational alignment, operations management, data management, and risk management.

Organizational alignment

Traditional department boundaries impede interaction on safety issues, inhibit the sharing of best practices, and limit integration among departments (such as sales and marketing, manufacturing, and customer service) that have incentive structures different from those of the safety organization. Many organizations lack a single individual with responsibility for the overall quality and integrity of safety processes and systems. Instead, authority—and accountability—are more diffuse than is necessary. Developing a team-based and product-focused staffing model made up of staff from the key functions—such as trial registration, regulatory, testing, and investigation—with a dotted-line back to their functional areas will break down departmental barriers and foster collaboration.

Operations management

Many of today's postmarket safety initiatives were either created in an earlier era or built organically over time. This ad hoc evolution has not resulted in a unified, structured, and adaptable vision to guide the management of safety-related processes. For example, the generation and dissemination of reports may continue even after they have been rendered obsolete by changes in regulation, technology, or business processes. This issue is common and can be addressed by building a continuous improvement framework into the organizations' operating model.

Drug safety operations also frequently lack standardized and aligned activities across product lines and across geographic locations, and thereby fail to leverage opportunities for standardization or economies of scale made possible by similarities in the overarching process. For example, when adverse event data arrives, it must be investigated and evaluated regardless of country, product, or source of the report. Lack of a unified operations structure can result in process redundancies or, worse, gaps—all of which create unnecessary risk.

Data management

Today's data systems often fail to capture, standardize, and integrate safety information efficiently. Furthermore, current adverse event reporting processes and systems typically lack a clear standard for quality of content. Companies often find that the safety data available to them in spontaneous reports is incomplete and lacks the information necessary to inform adequate analyses.

"Physicians working on a hospital staff use hospital-defined parameters for what constitutes an adverse event. Reactions the drug sponsor or agency might be interested in could be considered nonissues at specific facilities," said Beverly Kirchner, president and CEO of Genesee Associates and member of the board of directors of the Association of Perioperative Registered Nurses.

One estimate commonly cited by interview participants is that only about 10% of serious adverse events are reported. This underreporting is due to several factors: lack of clarity around what events should be reported, lack of available time, and poor recognition of adverse events because of differing standards or lack of training. For example, because there are many possible explanations for an adverse event, it is rarely possible to demonstrate a causal relationship between a compound and a specific adverse event.

Furthermore, the reporting fraction —the number of adverse events per drug that enters the pharmacovigilance reporting system—is often unknown or difficult to quantify with certainty. If 50 people on a given drug report chest pains, the number who actually experience chest pains could be much higher. And the company has no way of knowing just how much higher, which makes analysis difficult.

> "Postmarketing, spontaneous reports do not work in certain situations. For example, in the case of a common condition like heart disease, it is impossible to tell whether a case is related to a drug or whether it would have happened anyway. When the adverse event you're looking at is the same as or very similar to the manifestation or natural history of the very disease you are trying to treat, assessment of individual adverse events is not very helpful."
>
> Joanna Haas, M.D.
> Vice president of pharmacovigilance
> at Genzyme Corporation

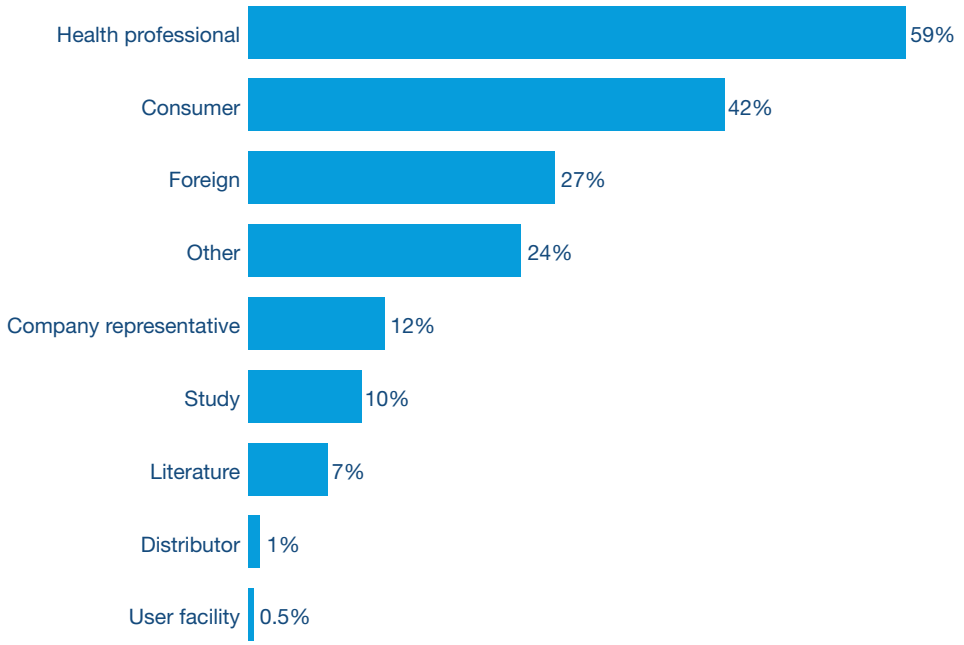
> "With spontaneous reporting, you know you're seeing only the tip of the iceberg. And from this tip you cannot event-gauge the full size of the iceberg."
>
> Jean-Louis Saillot, M.D.
> Vice president and head
> of global pharmacovigilance
> at Schering-Plough

Even when the data gathered are acceptably complete, analysis may still prove to be a Herculean task because of the myriad systems and institutions that store and report safety data. For example, more than 85% of U.S. physicians store their patient medical records on paper, and even those offices that are wired do not interface easily with pharmaceutical manufacturers.[9]

Much pre- and postmarket information is collected and analyzed in separate repositories. Data may be collected by different therapy- or compound-specific groups, by different means and for different purposes. Clinical trial data, for example, might not be leveraged for patient safety purposes simply because the trial data were not collected or stored with possible future uses in mind. Integrated analyses across departmental databases—analyses that could identify safety trends and facilitate more integrated reporting—are practically nonexistent simply due to the manner in which data are collected and stored (Exhibit 5).

"The challenge is how to connect the data that typically sits in different places; how to aggregate it into information on which the company can act," said Beth Ziemba, director of compliance management at Elan Corporation. "As an example, pharmacovigilance departments often use a different database than clinical departments do; linking these databases would allow a company to conduct improved analyses throughout product development, including postapproval."

Exhibit 5: Source of adverse event reports, 4Q04 through 3Q05



Source: *AERS Latest Quarterly Data Files, FDA.*

The hurdles in data sharing are significant not only within a company, but they also prevent data sharing between the company and the FDA, as well as across the broader scientific community. Further complicating the issue is that the safety information gathered within a single company that has locations in different countries may be owned and stored in the originating locations.

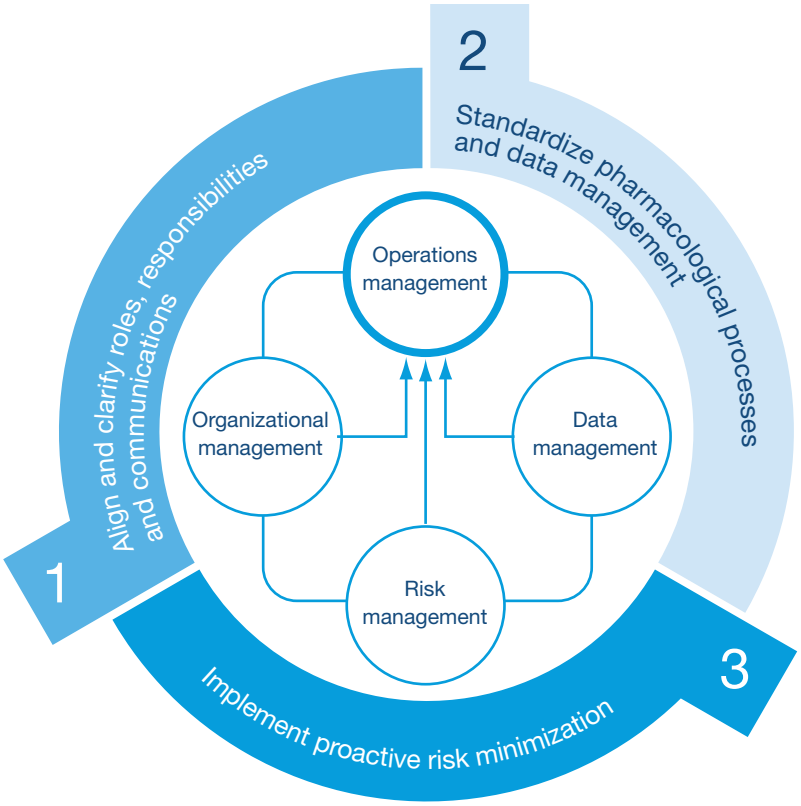
Risk management

Risk can take many forms: operational, financial, regulatory, and reputational, to name a few. To maintain stability within their core businesses, companies must be equipped to identify, evaluate, and manage those risks effectively. Too often, however, a company's risk management infrastructure is not integrated with its organizational, operational, and data management systems; there is overreliance on legacy policies and procedures, training, and documentation systems; and the company applies risk management in a reactive, inconsistent manner. The result of such inconsistent, nonsystematic, and uncoordinated approaches can be significant financial and reputational harm to the company.

Even those companies that have begun to use proactive risk management techniques in some functional areas have not used them consistently in areas pertinent to drug safety risk. For example, adverse event frequency data have been used for assessment of real-time risk. But these data typically are not integrated with measures of event severity, and so do not inform decisions through a predefined risk prioritization process.

> "There is a disconnect between R&D, clinical and postmarket surveillance. There should be a single repository where all data points, both pre- and postmarket, merge. This will drive more-efficacious drug safety monitoring and improve our ability to proactively discover potential safety issues before they become widespread."
>
> Noemi Romero-Kondos
> Global complaint management
> lead process manager at Hospira

The three strategies of effective pharmacovigilance



"For a pharmaceutical company to be successful, drug safety has to be at the core of all discussions across the organization. Pharmacovigilance has to be embedded into the day-to-day operations of the company. Similar to other systems, most of the issues around pharmacovigilance systems are not IT [information technology] issues but mainly process and people and organization issues. Tools, including IT solutions, must be implemented in the context of addressing process improvements and organizational needs."

Jean-Louis Saillot, M.D.
Vice president and head
of global pharmacovigilance
at Schering-Plough

Strategy 1: Align and clarify roles, responsibilities, and communications

Appropriate organizational alignment is a crucial enabler of the operating and data management models that govern the efficiency and effectiveness of a company's pharmacovigilance activities.

To establish an organization-wide pharmacovigilance program, companies should develop clearly defined safety roles and responsibilities that cover a drug from development through postmarket. This includes an unambiguous chain of command and an explicit escalation process for safety-related issues to prevent problems from dropping off management's radar. Decision-making models that are not hampered by poorly defined roles and responsibilities—as well as specific processes for handling safety-related issues—will drive clear accountability that will greatly mitigate safety risks before they develop into costly problems that could have been avoided.

"There is a pendulum movement right now to move beyond the fact that all medications have side effects and move more towards a focus on the benefits as well as the risks. We cannot assess the safety risks without a calculation in benefits."

Ludo Lauwers, M.D.
Senior vice president
Global head of benefit risk management, medicines and nutritionals sector
Johnson & Johnson

"There is a very limited pool of experienced people. Safety is moving to the forefront in companies, and companies are going to have to resource it better."

Judith M. Sills, Pharm.D.
Head of global safety intelligence
at Novartis Pharmaceuticals

Develop an objective, data-driven, team-based approach to risk monitoring and evaluation

Ultimate decisions on how to manage drug safety risks should be made by teams of key stakeholders. One approach would be to appoint stakeholders to a Data Safety Monitoring Board.

Another would be to establish a Drug Safety Risk Management Committee, formed early in the development process. By including representatives from discovery, drug safety, clinical development, legal, compliance, marketing and manufacturing, such a group enables more timely and complete safety issue identification, as well as more efficient and informed safety decisions.

Member identification, group formation, and membership transition (as the product moves through its lifecycle) should be standardized. Groups should feature diversity of perspectives based on criteria such as disease area, mechanism of action, and stage in the product life cycle.

Implement well-defined decision-making models, escalation processes, and communication channels.

A pharmacovigilance decision-making model should specifically define employee roles in gathering and analyzing information that ultimately influences drug safety decisions. Such a model allows employees to take greater ownership of pharmacovigilance issues, foster more collaborative relationships, and contribute to continuous improvement. For example, the model would allow employees to work autonomously within their roles while following a consistent method to determine appropriate action. In particular, a decision-making model would clearly establish ownership for specific decisions and would reduce ambiguity.

Companies should establish an escalation framework that ensures that issues are identified, prioritized, tracked, reviewed, and resolved in a timely manner. The framework would also empower employees to escalate issues to management.

For example, the framework would define a number of escalation criteria that—when matched together—would guide identified issues through a path from registration through to closure, with clear links to testing and investigation processes and regulatory reporting mechanisms. The criteria should be updated regularly based on a continuous improvement phase of the business process and ought to be based on regulation and historical experience with the particular product.

To operate effectively, both the decision-making model and the escalation framework require established, formalized communication channels. These channels enable employees, including those without direct drug safety responsibilities, to obtain necessary information from anywhere in the organization, to make informed safety decisions, and to communicate those decisions as appropriate.

Determine the pharmacovigilance workload, and sufficiently resource the required effort.

Companies also should provide sufficient resources to support their pharmacovigilance efforts, although individuals who possess the specialized skills necessary to execute drug safety activities are relatively scarce. To address this issue, some companies have embraced a staffing model that leverages diversified advanced degrees in pharmacovigilance functions such as signal detection, signal investigation, and risk management. Rather than relying solely on safety-related experience, nurses, pharmacists, and hospital technicians are enlisted for the more operationally focused functions such as processing forms, reporting, and case investigation.

Companies also should consider a mixture of fixed versus flexible resources, in which fixed resources with deep subject-matter expertise focus on specific products, while flexible resources cover a greater breadth of products. This staffing concept allows for temporary increases in the safety workload for a particular product and also facilitates optimal staffing in an environment in which drug safety is still viewed as a cost center.

Designate a pharmacovigilance operating model and business process owner.

One key resource is a designated process owner (not to be confused with the head of drug safety, although the drug safety head could be the process owner), who is responsible for the safety profile of the product and who acts as an unbiased steward of the overall operating model and principles of ensuring drug safety.

The individual would be accountable for the effective execution of the pharmacovigilance operating model and business process, would ensure that pharmacovigilance integrity and quality are kept consistently high, and would promote an atmosphere of continuous improvement.

In addition, the process owner should oversee internal communications that provide for connections between the safety function and marketing, sales, and other units whose primary responsibilities do not include safety. The responsibility for creating and enforcing appropriate safety checks, balances, and controls must rest with the process owner and be backed by senior managers who communicate the importance of safety to the entire company.

Ensure that appropriate process and organizational checks and balances are in place to limit bias and manage regulatory risk.

Because departments outside drug safety have different objectives and incentives, the importance of drug safety may not necessarily be understood or acted upon equally across a company.

"Companies have to be careful to ensure that independent, medically based decision making is adequately protected. Decisions on safety signals must be medically and science driven. In any situation, people have to be mindful of conscious and unconscious bias," said Saillot. "To ensure quality of decision making, we have to welcome checks and balances."

The responsibility for creating and enforcing pharmacovigilance checks, balances, and controls must rest, therefore, on management that has cross-functional oversight. For example, as part of a continuous improvement process, management would review the checks, balances, and controls with the process owner to ensure the process is working optimally. In addition, by actively supporting and communicating the importance of pharmacovigilance to the entire enterprise, executives can ensure organizational alignment around strong pharmacovigilance.

To ensure that these checks and balances are properly understood throughout the enterprise, furthermore, the cross-functional management team should foster a transparent collaborative working relationship between pharmacovigilance and corporate compliance programs.

In addition to the ensuring that the safety risks of the drugs in their portfolios receive the appropriate level of internal review, investors can see that an environment such as this one, that promotes compliance and transparency, demonstrates an increased level of accountability by senior executives. This can, in turn, be particularly helpful in the current environment—one in which corporate ethics, accountability, and responsibility all have been called into question.

The working relationship between pharmacovigilance and corporate compliance should be supported by quality assurance auditing and business unit monitoring processes that enable organizations to assess pharmacovigilance quality proactively and systematically, as well as by the level of systems that provide employees with an authoritative source of readily accessible and cross-referenced compliance information.

Strategy 2: Standardize pharmacovigilance processes and data management

Standardization around well-defined, integrated operations and data management processes is the salient feature of effective pharmacovigilance programs. This enables companies to ensure more-efficient patient safety, consistent regulatory compliance, and controlled risk management while ensuring scalability by consistently following a set of procedures. By the use of such consistent procedures, both trending and analysis can be performed on the same data set, and safety-related issues can therefore be compared easily.

Standardizing the sources, reports, and analytics used in the translation of data into safety signals allows for consistent event reporting and risk management decision making. Data standardization is also important because much information is collected and analyzed by discrete business units that have different therapy- or compound-specific working groups, different means of collection, and different uses in mind.

Several pharmaceutical companies standardize operational and data management activities in other areas, but very few have applied standardization to pharmacovigilance activities.

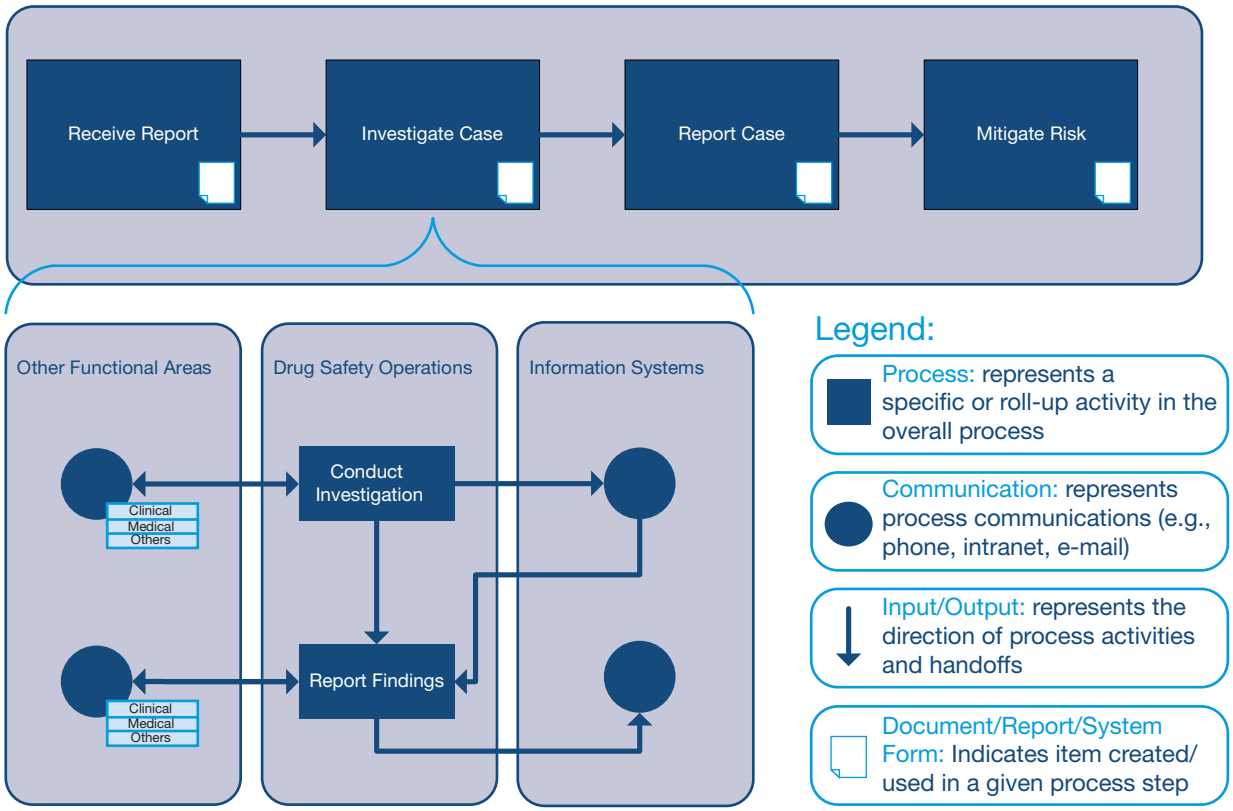
Align operational activities across departments and across sites.

A well-structured operations model provides a common and consistent platform upon which different geographic locations, functional groups, and product lines can refine their own site-specific processes, compare operational differences, and share best practices.

Safety profiles and regulatory requirements may differ from drug to drug and location to location. However, there are activities and decision points that can be standardized and aligned regardless of product or location. Additional levels of detail can be developed depending on products, locations, and organizational roles as one moves further into any one area (See Exhibit 6).

Accordingly, the fundamental safety reporting process should be common from country to country, though it should also be able to accommodate local regulatory requirements or cultural imperatives. Such standardization can help pharmaceutical firms cope with the regulatory requirements of the multiple jurisdictions within global markets and can foster sharing of best practices.

Exhibit 6: Operations model for pharmacovigilance processes



Implement process-driven standard operating procedures, work instructions, and training materials. Standardization of work instructions, training materials, and documentation drives greater adherence to quality processes and enables companies to cope with the loss of key employees, which is especially important in the face of a relatively limited drug safety talent pool.

Pharmacovigilance model and process fundamentals training—training on the highest level in the pharmacovigilance model and process—should cover the overall processes, organizations, and systems and should remain the same regardless of a person's role in the safety organization. This can also be a useful tool in raising awareness throughout the organization.

More-customized training for each role in the safety organization should drill down from the fundamentals training into specific roles and responsibilities. Trainers, therefore, can efficiently mix and match training modules as appropriate to create role-specific and product-specific training materials that build upon what employees learned during fundamentals training.

"It is extremely difficult to find pharmacovigilance-qualified M.D. candidates. You really have to build an infrastructure that can train and mature them in-house."

Jean-Louis Saillot, M.D.
Vice president and head
of global pharmacovigilance
at Schering-Plough

"We don't view drug safety from a postmarket or premarket perspective but, rather, as a continuum from the time the compound is identified and the time of animal studies on through when companies are hoping to get approval. This is far more involved than looking separately at postmarket and premarket."

Alan Goldhammer
Associate vice president of
regulatory affairs for the
Pharmaceutical Research and
Manufacturers of America (PhRMA)

Integrate safety data through data and system interoperability standards.

A single database should include data across the entire product life cycle—both premarket and postmarket. By viewing postmarket safety as a component of a continuum and by performing analysis of safety data across this continuum, organizations can identify more safety signals.

"Integration of data is important to perform signal detection across a product's development life cycle," said Ziemba. "Integration would include the tools to pool data from the variety of data sets across the company—including data on product complaints and sales and marketing information—and from data sets housed externally, so as to create an aggregate data set that is as close to complete and as inclusive as possible."

There are, however, several challenges to integration across the safety continuum—mostly around data and system interoperability standards. In both pre- and postmarket operations, multiple databases may contain similar information, but these databases typically are neither linked nor linkable to each other. Each database is designed and populated for different objectives and therefore contains nominally different but inherently similar safety data elements. For example, some databases may be created for preclinical toxicology and pharmacology studies, some may be created for each clinical trial and some may be created for each postmarket use (e.g., complaint management, customer service, or medical communications).

Despite the fact that different databases have different uses, their data contains many common safety-relevant elements. Companies can link these databases (and thereby facilitate integrated safety analyses) by creating standards around the database elements as well as data formats, terminology and system interoperability.

Many of the same standardization issues posed by data sets housed internally are similar to the issues posed by external data sets such as automated claims databases, physician records, pharmacy records, and clinical registries. As within the company, a common format, common data elements, common terminology (such as MedDRA), and system interoperability standards can facilitate linkages among safety data. While little can be done to standardize external data without the efforts of groups such as the ICH, companies can improve their own management of data obtained from internal and external sources by adopting in-house data and interoperability standards.

Implement work flow management technology to ensure appropriate transparency and accessibility of safety information.

Work flow management technology already has created value in other areas of the pharmaceutical value chain—such as in help desk functions and electronic capital expense requests—and consequently is gaining widespread industry acceptance. Applied to pharmacovigilance, this technology can identify and distribute information to stakeholders according to a predetermined set of rules—such as product family, type of safety event, and event severity—and thereby facilitate effective and consistent management of safety reporting and data sharing.

Work flow management systems ensure that only the appropriate employees receive the data required to inform the decisions they are authorized to make within the pharmacovigilance model. The technology also ensures that the appropriate decision, sign-off, communication, and retention requirements are executed and documented—a process known as work flow close out. The technology, therefore, allows for more-controlled management of tasks, thus ensuring that all safety events are handled appropriately.

Select a vendor that best matches the pharmacovigilance operating model, business process, and vendor/system selection criteria.

Companies recognize that software and technology vendors have made significant advances in safety data mining, in analytics, and in other tools required for successful pharmacovigilance programs. Technology solutions must not drive companies' pharmacovigilance processes or operating models, however.

Technology should instead bind the operating model with the organizational model, supporting risk management activities throughout the safety organization. To identify the tools and technologies that are most appropriate to an organization's unique needs, companies should derive system requirements from process-based business rules and feed those requirements into a systematic vendor selection process.

Within the industry, two concerns have arisen about information technology vendors. First, software solutions are expensive, and second, off-the-shelf solutions are neither customizable nor flexible enough for an organization's unique requirements. Companies planning to customize technology should undergo a thorough search process for the right vendor and product. Some companies will find that a homegrown technology solution is the best option, while others will find that off-the-shelf solutions work better.

"Safety is an evolving area, which is why software is such a challenge. If you build a tool for today's requirements, the system is static. Safety regulations and safety thinking continue to evolve, so a system that will serve that area has to be dynamic and flexible," said Sills. "Vendors are out there, but I don't know if there are any dominant vendors. I think that companies, as they get frustrated, resort to building their own systems."

In the event of technology gaps, process workarounds can ensure that the integrity of the process and technology solution remains intact, whether the product is off-the-shelf, customized, or homegrown.

> "Comprehensive software is just now slowly developing and has not yet matured. However, it is still important for companies to query technology companies about developing software to link and evaluate all safety data."
>
> Tobias Peschel, M.D., Ph.D.
> Vice president of drug safety
> and public health
> at Gilead Sciences

Best practices: Technological concepts for enhanced pharmacovigilance

System Capabilities

Systems should accommodate safety information in multiple formats from both direct sources—such as consumers, physicians, pharmacies, and other third parties—and indirect sources, which include regulatory agencies, electronic medical records, and payer automated claims databases. Systems should also share drug safety information across departments and route that information to the right stakeholders at the right time, in the right format and with the right level of privilege. Further capabilities should include the performance of leading-edge safety diagnostics and analytics as well as the generation of periodic and ad hoc reports for both internal and external consumption.

System Requirements

To support these capabilities, systems should employ data standards—such as the CDISC safety data standards—that facilitate the transfer of data and multisystem analysis of distributed safety data, as well as a medical data dictionary such as MedDRA to support the classification, retrieval, presentation, and communication of medical information to internal and external stakeholders.

Technology Features

- Branching that uses initial responses and specific conditions reported during data entry to collect specific diagnosis information
- Prepopulated data fields that facilitate the diagnosis of suspected safety events—such as specific reactions or symptoms of the event—and that lead to data that is more useful during investigations, analytics, and monitoring
- Data filters that adhere to and satisfy specific regulations such as HIPAA privacy rule regulations
- Data analytics that link data sets and facilitate pattern recognition and detection
- Work flow features that facilitate the controlled routing of events and safety data to the appropriate organizational and scientific stakeholders
- Event- and threshold-based triggers, with a prescribed corrective action and approval process

Strategy 3: Implement proactive risk minimization

In the context of pharmacovigilance, a risk management framework should have three fundamental traits:

- Ability to quickly identify risks based on internal and external information, through processes that identify and extract compound- and indication-specific information from across the organization
- Categorization and ranking of the overall organizational impact of safety risks based on the company's risk appetite and tolerance
- A predefined process that manages risks and that involves internal stakeholders who both develop the risk management plans and periodically revalidate pertinent algorithms and decision criteria

An essential first step is to ensure that appropriate controls for regulatory compliance are in place. Companies should carefully document and drive compliance with all policies and procedures. Maintenance of records is important, especially those of past audits and corrective and preventive action plans (CAPAs). Companies should enforce policy and procedure retirement dates and update processes to ensure that they meet current legal and regulatory requirements.

Beyond these fundamental compliance measures, companies must inject objectivity and standardization into risk management by identifying risk tolerances and priorities and developing comprehensive mitigation plans in advance of drug safety events.

"For effective risk management, the pharmacovigilance risk identification function alone is far from being enough," said Saillot. "It's just one of the first steps. For risk minimization activities to be effective, everyone must be aligned and acting on identified risks."

Develop risk management action plans based on preestablished risk scoring and mitigation processes.

Established risk scoring and mitigation processes can ensure objectivity and standardization. Risk scoring should be based on a combination of industry benchmarking, corporate risk tolerance, and internal assessments via a set of predefined algorithms that allow for objective evaluation of specific issues and actions. For example, the risk impact on individual products may be determined by the measurement of diverse data points such as number of adverse events per product family, patient demographics, and overall portfolio value of the product and product family. Issues may be assessed either for each product individually or for a class of products and should be continuously updated as the environment necessitates. As part of the assessment, companies should evaluate both external risk factors—such as regulatory, reputation, and product liability risk—and internal risk factors—such as portfolio, strategic, and financial risk—when examining specific risk events.

Companies similarly may assign scores to inform the risk tolerance and risk appetite levels for specific types of drug safety issues across the product portfolio. Based on these predefined levels, the company can develop appropriate risk mitigation plans.

For example, pharmacovigilance groups can work to develop an objective, standardized approach to investigation of safety signals from the point of initial detection. Standardization of the investigation approach is essential, from hypothesis generation through hypothesis testing and, ultimately, to the process of making final risk mitigation decisions. Companies that employ analyses and reports via a standardized, predetermined approach can make consistent and appropriate decisions regarding risk communication and action. Such an approach to risk management will help companies reduce reactionary measures and potentially costly and ineffective decisions made under real-time duress.

Implement data mining techniques to bolster safety analytics, reporting, and investigation.

As mentioned earlier, effective management of safety data across multiple platforms is critical to effective management of safety events. This same data can be mined to supplement existing safety detection methods and help assess the patterns, time trends, and events associated with drug interactions. Dynamic and flexible analytic software and the use of new tools, such as biomarkers or pharmacodynamic markers, also can help companies maximize the benefits of medicines while minimizing safety risk.

The rationale for data mining is clear: Detection of most safety signals is difficult. While serious and unlabeled adverse event signals are relatively straightforward, the more difficult signals require analysis across a number of data sets. This is an extremely time-consuming task if performed without the aid of data mining technology, which allows for the systematic examination of data with statistical or mathematical tools to determine whether a potential safety signal warrants further investigation.[10]

Data mining typically supplements and supports existing safety signal detection methods and is especially useful in assessing the patterns, time trends, and events associated with drug-drug interactions. It is an effective exploratory and hypothesis-generating tool that can provide insights into the adverse event reporting patterns for a given product relative to other products in the same therapy class.[11] It also can indicate the existence of issues around the mechanism of action—such as receptor specificity and selectivity, signaling pathways, and intracellular protein interactions. It is the integration of the safety signal data combined with an introspective evaluation of known risks based on internal data that provides the greatest value in an analysis of the true impact of drug safety issues.

Using the problem-oriented approach as a pharmacovigilance business model

Several companies have incorporated the spirit and intent of proactive risk management into their development processes. Joanna Haas, M.D., vice president of pharmacovigilance at Genzyme Corporation, calls Genzyme's system the "problem-oriented approach" to drug safety and pharmacovigilance. In essence, the company looks for the potential risks of its compounds from the time of discovery through preclinical development, and thereafter via postmarketing surveillance. "If you think drug interactions may be an issue, you'd make that something you look for," Haas said. "To designate something as a potential safety problem presumes you're trying to find the answer, which may be that there is in fact no problem." Haas went on to say that including risk concerns as well as benefits in filings and discussions with the FDA makes the approval process go more smoothly.

Incorporate continuous improvement activities and standardized risk communication plans.

Continuous improvement activities should include new safety risk information to inform changes to the risk profile that might further minimize product risks and maximize benefits for the targeted patient population. Continuous improvement activities also should include reevaluation of risk criteria around new internal or external factors that may influence overall risk appetite and tolerance.

Communication of drug safety risk information both internally and externally is perhaps the most critical output of pharmacovigilance risk management activities. Communication plans should describe the risk escalation and communication processes both within and outside the company. To ensure that messages disseminated are accurate, consistent, and not subject to misinterpretation, the drug safety officer, the chief medical/scientific officer, and the public relations, legal, regulatory, and compliance executives should be involved in message design and deployment.

All communication plans should consider the audience involved, especially when that audience is composed of the patient- or physician-centric communities that have such a high impact on industry reputation. Sales representatives, for example, can play a key role in communicating risks to physicians. "There is a role for sales reps to objectively give information to physicians on the benefits along with the risks of products," said Ludo Lauwers, M.D., senior vice president and global head of the benefit risk management, medicines, and nutritionals sector at Johnson & Johnson. "If a product has an issue, it is important to educate. I know it sounds like a contradiction as sales reps have an incentive to sell, but we have used sales reps in the past to go to physicians with educational safety messages. It works very well because it is a strong way to make sure that an important safety message is conveyed to physicians."

Create a dashboard that summarizes and promotes timely awareness of safety risks across the portfolio and timely execution of safety risk minimization activities.

A robust signal detection and action platform, enhanced by data mining techniques and enabled by a cross-functional team-based approach and the right communication plans, still has a number of limitations. It is difficult for the pharmacovigilance process owner to ensure that all the correct actions are taken in a given situation.

One of the most effective practices for dealing with this challenge is a customized safety risk dashboard that provides a single, real-time, authoritative information source for all risks across the company's portfolio of products.

The dashboard should include overall safety histories, short- and long-term information on use, case-by-case reporting, expected reactions versus actual adverse events, and a product's regulatory reporting history. Based on data gathered from the dashboard, specific risk mitigation procedures tailored to a given type and level of risk may be accessed and followed for guidance in a timely and effective manner.

Dashboards facilitate proactive management of safety risks by summarizing safety information across the product portfolio in real time and by identifying the types of data that should and should not be used in drug safety decision making. Dashboards are key means of ensuring that risk management and communication plans are executed in a timely and effective manner.

Conclusion

The time for companies to reexamine their pharmacovigilance practices and to develop and implement effective, best-in-class solutions is now. Many organizations have already begun to evaluate and enhance their pharmacovigilance practices for efficacy and efficiency, and through that experience many have encountered significant obstacles.

We believe that the practical approach we have discussed in this paper can provide a fresh perspective, both to those companies that have just begun the journey and to those that have encountered obstacles along the way. We have provided a framework that will enable companies to find success by concentrating on the integration of operations, risk management and the supporting organization. The power of this approach lies in the alignment of strategy with accountability and in the linkage of functional areas within a single integrated operating model that adapts more easily to the changing characterizes of the industry, regulators and the public alike.

By concentrating on integration across the key infrastructures, companies will enable themselves to avoid the challenges companies typically face when building toward the future. They will create a sustainable infrastructure and a highly adaptive culture, both of which can lead to greatly diminished costs and risks, as well as greatly improved outcomes for patients.

> "Timely communication of emerging risks to physicians and patients, as well as regulators, is extremely important. Everyone who is prescribing, dispensing, or taking a drug needs to be informed of potential risks as early as possible."
>
> Tobias Peschel, M.D., Ph.D.
> Vice president of drug safety
> and public health
> at Gilead Sciences

Endnotes

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11 Portions from "Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment," FDA Guidance to Industry.

Glossary

ADR: Adverse Drug Reaction (see Adverse Event).

AERS: Adverse Event Reporting System – FDA's database of reported adverse events.

Adverse Event: Any undesirable experience associated with the use of a medical product in a patient

Background Rate: Refers to the background rate of occurrence for an adverse event in the general population or in a subpopulation with characteristics similar to that of the exposed population. Often compared against the Incidence Rate. (See also Incidence Rate, Reporting Rate and Safety Signal).

Biomarkers: Physiologic indicators (e.g. blood protein levels) that can be used to measure the progress of a disease, outcomes of administration, and/or the positive/negative effects of a treatment, sometimes long before other indications or symptoms are apparent. (See also Critical Path Initiative).

CAPA: Corrective and Preventive Action

CDISC: Clinical Data Interchange Standards Consortium – Organization that establishes and supports worldwide, platform-independent industry data standards to support the electronic acquisition, exchange, submission, and archiving of clinical trials data and metadata that enable information system interoperability for medical and pharmaceutical research and development and related areas of healthcare. [www.cdisc.org]

Clinical Registry: (see Registry).

Data Mart: (see Data Warehouse).

Data Mining: Systematic examination of data using statistical or mathematical tools to determine a potential safety signal warranting further investigation. Typically used to supplement existing safety signal detection strategies, data mining is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. It is not used to establish causal relationships between products and adverse events, but rather as an exploratory or hypothesis generating tool that may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products. (see also Safety Signal)

Data Warehouse: (Sometimes referred to as a "data mart") a repository of integrated information, extracted from heterogeneous data sources, available for efficient querying and reporting that supports data analysis and decision making tasks.

EDC: Electronic Data Capture

EDR: Electronic Data Record

EMR: Electronic Medical Record

Expected Adverse Event: (see Adverse Event)

Good Pharmacovigilance Practices: FDA Guidance on current generally accepted good pharmacovigilance practices for post-market safety vigilance activities [www.fda.gov/cber/gdlns/pharmacovig.htm]

HIPAA: Health Insurance Portability and Accountability Act (1996), which required the Department of Health and Human Services (HHS) to adopt national standards for electronic healthcare transactions. The HIPAA Privacy Rule provides federal protection for the privacy of individually-identifiable health information (also known as protected health information [PHI]) by prohibiting the use and disclosure of PHI except to the individual subject and to HHS – unless specifically permitted. (See also HIPAA).

HL7: Health Level Seven, an ANSI-accredited Standards Developing Organization which produces standards, specifications, and/or protocols for clinical and administrative healthcare data. [www.hl7.org] (see also NCPDP).

ICH: International Conference for Harmonisation – Organization where regulatory authorities of Europe, Japan, and United States and experts from the pharmaceutical industry discuss scientific and technical aspects of harmonizing activities across the lifecycle of pharmaceutical products. International harmonization efforts around Medical Terminology (MedDRA), the Common Technical Document (CTD), and Electronic Standards for Transmission of Regulatory Information (ESTRI) have been coordinated under the sponsorship of the ICH. (see also MedDRA) [www.ich.org]

Incidence Rate: Rate at which new cases of adverse events occur in the product-exposed population. The numerator consists of the number of new cases. The denominator consists of the number of exposed patients and time of exposure/time at risk. There are inherent difficulties in calculating incidence rate for spontaneous events due to the uncertainty around the number of adverse events not reported. Oftentimes compared against the Background Rate (see also Background Rate, Reporting Rate, and Safety Signal).

Labeling: (see PI – Prescribing Information / Package Insert)

Labeled (Expected) Adverse Event: An adverse event that is one of the known adverse events listed on the product package insert (PI)

Large Simple Safety Studies: (see LSSS)

LSSS: Large, Simple, Safety Studies – Randomized clinical studies designed to assess limited, specific safety outcomes in a large number of patients. These outcomes – generally important safety endpoints or safety concerns suggested by earlier studies – are defined a priori with the study specifically designed to assess them.

MedDRA: Medical Dictionary for Regulatory Activities – International standard of medical terminology, developed under the auspices of ICH, used for regulatory activities. MedDRA is particularly important in the electronic transmission of adverse event reporting, both in the pre- and post-marketing areas, as well as the coding of clinical trial data. [www.ich.org] (see also ICH).

MedWatch: FDA Safety Information and Adverse Event Reporting Program that allows healthcare professionals and consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use. Reporting can be done online, by phone, or by submitting the MedWatch 3500 form by mail or fax. [www.fda.gov/medwatch/]

NCPDP: National Council for Prescription Drug Programs – ANSI-accredited Standards Development Organization (SDO) which creates and promotes standards for the transfer of data to and from the pharmacy services sector of the healthcare industry. [www.ncpdp.org] (see also HL7)

Non-Serious Adverse Event: All adverse events not classified as a serious adverse event

Pharmacoepidemiology: Study of the utilization and effects of drugs in large numbers of people. To accomplish this, pharmacoepidemiology borrows from both pharmacology (study of the effect of drugs) and epidemiology (study of the distribution and determinants of diseases in populations). [www.pharmacoepi.org]

Pharmacovigilance: Scientific and data gathering activities relating to the detection, assessment, understanding and prevention of adverse events – including, to the extent possible, understanding the nature, frequency, and potential risk factors of the adverse events.

PHI: Protected Health Information (see also HIPAA Privacy Rule).

PI: Prescribing Information / Package Insert – Prescription drug product's FDA approved labeling which contains a compilation of information about the product, including information necessary for safe and effective use.

READ Codes: United Kingdom's National Health Service (NHS) Clinical Terms. Combined with SNOMED-RT to create SNOMED-CT (SNOMED Clinical Terms). [www.nhsia.nhs.uk/terms/pages/] (See also SNOMED).

Registry: An organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a common factor that predisposes them to the occurrence of a health-related event. This common factor may include exposure to a specific medical intervention, a particular disease, condition, or risk factor, or substances (or circumstances) known or suspected to cause adverse health effects.

Reporting Rate: (see Incidence Rate).

RiskMAP: Risk Minimization Action Plan – A strategic safety program designed to meet specific goals and objectives in minimizing 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 these goals. [http://www.fda.gov/cber/gdlns/riskminim.htm]

Safety Signal: An excess of adverse events compared to what would be expected to be associated with a product's use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event, whether the product represents a potential safety risk, and/or whether other risk mitigation actions should be taken. (See also Incidence Rate, Reporting Rate and Background Rate).

Serious Adverse Event (SAE): An adverse event that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolonged hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/ birth defect, or requires intervention to prevent permanent impairment and/or damage. [www.fda.gov/medwatch/]

Signal Detection: Detection of a safety signal (see also Safety Signal).

SNOMED: Systemized Nomenclature of Medicine – Universal healthcare terminology that enables clinicians, researchers, and patients to share healthcare knowledge worldwide across clinical specialties and sites of care. SNOMED RT and NHS Clinical Terms Version 3 (READ Codes) were combined into SNOMED CT (Clinical Terms) – a single, global health terminology with a comprehensive structure to support electronic health records). [www.snomed.org] (see also READ Codes).

Spontaneous Report: Unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Poison Control Center) that describes one or more adverse drug reactions in a patient (not deriving from a study or organized data collection scheme) who was given one or more medicinal products.

Unexpected Adverse Event: (see Adverse Event)

Unlabeled (Unexpected) Adverse Event: An adverse event that is not one of the known adverse events listed on the product package insert (PI)

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