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The Evolving Role Of Pharmacovigilance

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New global regulations have forced the concept of pharmacovigilance to expand beyond just identifying adverse events. Today pharmacovigilance is on the minds of every pharma and bio executive, and it starts earlier in the drug development process. To gain an understanding of the current state of pharmacovigilance in the industry, Life Science Leader spoke with Sujith Eramangalath, the senior analyst in medical imaging, healthcare IT, and life sciences IT at Frost & Sullivan; Drew Kilpatrick, Ph.D., director of global safety and pharmacovigilance at Kendle; John Loucks, VP of Oracle Health Sciences; Nayan Nanavati, M.S., M.T., VP and general manager, peri- and post-approval research and worldwide head of pharmacovigilance at PAREXEL; and Charles Saldarini, CEO of Sentrx.

What Are The Trends In pharmacovigilance?

Drew Kilpatrick, Kendle: A key change in thinking for those working in pharmacovigilance is the realization that the benefit-risk assessment is the ultimate driver for patient safety and not simply the frequency of adverse event types. The initial risk/benefit assessment at the time of marketing application is made with limited information and is based on a relatively homogeneous population, often based on restrictive entry criteria dictated by the inclusion/exclusion criteria of the phase I to III studies in the clinical development program. As a consequence of this greater awareness, improvements have been made in the gathering, reviewing, and reporting of patient safety information.

John Loucks, Oracle: Risk evaluation and mitigation strategies (REMS) and risk management programs (RMPs) are the leading topics in today's evolving industry. Consequently, pharmaceutical companies are increasingly adopting signal management solutions to help them support their risk management activities.

There is also a shift from "post-market" surveillance to full-spectrum monitoring of a drug. Pharma can and must monitor safety throughout a drug's entire life cycle — from clinical development all the way through patient care. In the near future, we will begin to see pharmaceutical companies leveraging technology to facilitate end-to-end monitoring and even gain the ability to monitor safety directly from electronic medical records (EMRs).

Nayan Nanavati, Parexel: There is a growing trend toward incorporating more pharmacovigilance activities into biopharmaceutical product development. Historically, assessment of safety and efficacy occurred during the marketed life of a biopharmaceutical, and now there is a new shift toward conducting ongoing risk/benefit analysis over the entire product life cycle, including from first-in-human studies through the product's end of life in the market.

Another trend is to collect a larger amount of data in order to identify patterns of safety-related issues. This trend for more data collection along with regulations that require the implementation of risk management plans at the time of submission is indicative of a new level of effectiveness in proactively managing compounds in development.

Charles Saldarini, Sentrx: We think the key trend is what we call "new safety." By that we mean an increased emphasis on collecting and examining safety in a manner that is more directly aligned to the long-term value of the drug commercially, beginning with early phase clinical trials and continuing into post-approval phase. Sponsors who maximize their knowledge of their drug's pharmacovigilance profile and integrate it into their commercial planning will have greater influence with regulators, payers, and ultimately patients and prescribers. We think this is particularly true of the increasing number of specialty drugs under development. This trend is very different from an older or more traditional view of safety as a compartmentalized regulatory function that is purely process driven. As a result, we believe there will be a greater demand for safety expertise at all phases of the product's life cycle.

What Tools Can Pharma Companies Employ To Effectively Manage The Review, Processing, And Response To Adverse Events Signals?

Sujith Eramangalath, Frost & Sullivan: According to our estimation, the average spend on pharmacovigilance will be 6% to 8% of pharma companies' total 2008 R&D spend. This will vary from region to region. It is believed that spending is high in the North American region, predominantly in the United States, followed by the European countries. So, drug detection systems and case processing solutions are the key tools to effectively manage the review and processing of adverse events.

Drew Kilpatrick, Kendle: Fortunately, several proprietary databases are available for warehousing safety data which also allow direct electronic reporting to regulatory authorities or the printing of CIOMS (Council for International Organizations of Medical Sciences)/MedWatch forms for submission to regulatory authorities which do not accept electronic reports. Agreement on MedDRA as the universal coding dictionary makes it possible for signal detection software to analyze standardized coded internal and external event data. Standardized regulatory report templates such



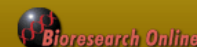
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as the risk management plans and annual safety reports (for clinical trials) make it easier to understand and quantify the significance of adverse event signals, making it easier to put any signal into context.

John Loucks, Oracle: The FDA estimates that less than 10% of all adverse events are actually reported, yet pharmaceutical manufacturers are still drowning in a sea of reporting obligations. Efficient safety systems can help pharmaceutical manufacturers manage this burden. It is important to note that medical effectiveness is even more important than operational efficiency in the pharmacovigilance process. After all, what good does it do to submit spontaneous and periodic reports on time when a manufacturer may never have the opportunity to analyze what the data actually may indicate?

This is where signal management technology becomes so important. A database can compile data, and a simple signal detection tool can help identify real and false signals. However, only a "structured signal management" approach with a defined workflow and integrated processes provides the framework required to turn reams of raw data into medical information. After all, the goal is not to simply report adverse events on time, nor to simply detect signals. The goal is to continually monitor and improve a drug's risk/benefit balance with the benefit of enhanced data to support a conclusion.

Charles Saldarini, Sentrx: It is less about specific tools than it is about the integration of people, processes, and technologies that produce longitudinal solutions that can be applied over a drug's life cycle. Certainly there are many different tools available today that help, such as greatly improved databases and very powerful data mining tools integrated with visualization technologies that all make examining large volumes of safety-related data faster. However, no one tool can be substituted for the insights provided by a comprehensive analysis performed by a pharmacovigilance expert.

Is Pharmacovigilance Becoming Even More Important Now In The Pharma/Biopharma Industries? Why?

Sujith Eramangalath, Frost & Sullivan: With the ever-mounting pressure from the regulators, pharma companies are being forced to streamline various reporting procedures and ensure that safety reports are processed in an accurate and timely manner. This would require the synchronization of adverse event reporting and various other reports, such as electronic submissions, and document management tools. Pharmaceutical companies are already seeing the need to modify their existing process structures and systems to adhere to the set protocols and standards. Several regulators like the EMEA (European Medicines Agency) have already implemented various structures and models for the pharmaceutical companies and regulators to submit adverse event reports electronically in specific formats such as E2B (electronic safety reports). This would be a major driver for adoption of pharmacovigilance solutions.

Drew Kilpatrick, Kendle: Yes, for both pre- and postmarketing phases of clinical drug development. In the preregistration phase, the primary focus traditionally has been to confirm efficacy of the investigative medicinal product (IMP). Establishing the safety profile of an IMP in development has often been considered as a secondary requirement. However, earlier development of the risk management plan and the annual safety report promotes safety as an equal partner with efficacy in the clinical development of the IMP. Similarly, the requirement to confirm, maintain, or improve the risk/benefit outcome for a marketed product places greater emphasis on the timely collection and reporting of patient safety information. In an electronic age, when both the providers and regulators are replacing paper with electronic solutions, pharmacovigilance within pharma/biopharma must be more proactive and innovative in understanding their safety data if they are to identify changes in the safety profile before regulatory agencies.

Nayan Nanavati, Parexel: Today, with bioengineering and more sophisticated development methodologies available, the industry is developing more complex biopharmaceutical compounds. Furthermore, the industry is now evaluating targets for much more complex multifactorial and chronic diseases. As we approach this new development frontier, we will need to learn about how compounds will behave in regard to such complex diseases.

Since the industry knows little about these compounds and targets, this will necessitate biopharmaceutical companies to be more proactive and vigilant about safety-related issues from the first time compounds are introduced in humans to the end of the product life.

Biopharmaceutical companies cannot afford to have products fail and must ensure a product is terminated in its development as early as possible due to safety-related issues. Therefore, there is growing interest in learning about potential safety issues as early as possible.

Charles Saldarini, Sentrx: We believe it is certainly becoming more important. A full safety profile is an evolving dynamic, and those manufacturers who build strong bases of knowledge during the clinical phase and then continue to augment and improve their understanding will establish the greatest commercial leverage. If you think of this in terms of current regulatory emphasis about outcomes and comparative effectiveness and current payer focus on value, along with a population that consumes more medications concomitantly, understanding all aspects of the product profile and continued research regarding what can be improved about the product are critical.

What Are The Biggest Pharmacovigilance Needs Of Pharma/Biopharma Companies?

Sujith Eramangalath, Frost & Sullivan: Most of the pharmaceutical companies are plagued with systems that do not envelop all of the adverse events tracking processes end-to-end. This has resulted in severe inefficiencies and the requirement of regular audits to maintain a high degree of quality. In order to adhere to the strict regulatory guidelines set forth by the various agencies, the pharmaceutical companies are required to streamline and automate their adverse event management systems.

The big and medium pharma companies need to invest heavily on case processing systems and the biotech, and generic manufacturers need to invest heavily on services such as call centers to track adverse drug events.

Nayan Nanavati, Parexel: Overall, biopharmaceutical companies must realize that product safety in the marketplace can be preserved only if patient safety is foremost. As the industry is aware, the FDA has authority through the FDAAA to require a risk evaluation and mitigation strategy (REMS) at the time of filing, and the EMEA has already had such a requirement in place. Furthermore, with the new authority that the FDA has been granted now to impose civil penalties and product withdrawals, biopharmaceutical companies must ensure that their risk management plans are well thought out and incorporate all aspects of preclinical as well as product-class-related safety issues.

With the new emphasis on risk mitigation and communications through the REMS initiative, biopharmaceutical companies need to have effective communications plans in place to disseminate safety-related concerns in a comprehensive way for the patient, payer, and pharmacist communities and evaluate these communications on an

ongoing basis for their effectiveness.

Charles Saldarini, Sentrx: One of the biggest needs is the ability to resource pharmacovigilance solutions in an effective and efficient manner. Adverse events are relatively unpredictable, so companies wrestle with the right ratio of fixed to variable resources required to meet their needs across the pharmacovigilance spectrum. This includes classic case processing, but really extends into the complexities of aggregate reporting, partner management, safety systems, and risk management.

Could Social Media Play A Role In The Future Of Pharmacovigilance?

Drew Kilpatrick, Kendle: Yes; social media, by promoting pharmacovigilance and its importance/relevance to consumers and patients, could create an environment whereby these groups do not feel uncomfortable or view it as a waste of time to report adverse events they have experienced to their healthcare providers or to the marketing holder. No adverse event should be considered trivial by the consumer, patient, healthcare provider, or the marketing holder.

John Loucks, Oracle: Social media has a role in pharmacovigilance. It provides a forum for exchange of best practices, knowledge sharing, and collaboration. Today, we see social media beginning to be leveraged to communicate the benefits of drugs. It can also play an integral role in driving awareness of risk.

Charles Saldarini, Sentrx: It's possible. However, there are regulatory requirements sponsors must either clarify or develop comfort with in order to tap social media channels effectively.

What's The Biggest Challenge To Tracking Adverse Events During Clinical Trials?

Sujith Eramangalath, Frost & Sullivan: The majority of the data for determining the cause-effect relationship that exists between treatment and outcomes is collected in the phase III stage of clinical trials. However, the majority of studies do not have optimal designs as the number of patients participating is limited, and it is difficult to identify adverse events that occur rarely. At the same time, the short duration of trials makes it difficult to track adverse events with long latency. Another limitation of clinical trials is the population in which a drug is tested. The characteristics of the participants do not always correspond to the characteristics of the population in which it will later be used.

Drew Kilpatrick, Kendle: One of the major challenges to tracking adverse events occurring in clinical trials relates to ensuring compliance with global data protection legislation. This has meant that it is no longer acceptable to use patient initials, date of birth, etc. as an identifier in some countries. However, patient identifiers are needed to map adverse events back to the appropriate patient.

John Loucks, Oracle: One of the key challenges to tracking adverse events is that many departments have traditionally operated as independent silos. Traditionally, various clinical, pharmacovigilance, and other groups have duplicated efforts, lacked collaboration, and failed to implement the most efficient clinical development processes. Duplicate data is often kept in multiple databases, resulting in inefficient resource usage, compromised data quality, and significant reconciliation challenges. This approach does not work in the best interest of the pharmaceutical company, the physician, or the patient, who ultimately carries the burden of this lack of alignment.

Charles Saldarini, Sentrx: Certainly an issue our clients, and by extension the industry, wrestle with is developing approaches and integrating technologies to make clinical trial management both robust and user-friendly. The continuing adoption of electronic data capture and its integration into adverse event management is a related issue we deal with frequently as clients work to ensure accelerated reporting requirements are met efficiently. Continuously updating site investigators about changes in the emerging adverse event profile is another issue.

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