Pharmacovigilance at the Intersection of Healthcare and Life Sciences
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Pharmacovigilance and safety surveillance has evolved from yesterday’s focus on transactional activity and information flow to today’s awareness of the importance of risk management and proactive signal detection. Risk management activities have come to the fore as the focus of good pharmacovigilance expands beyond data collection to drug safety surveillance models that have a more inherent value. This evolution will continue as the trajectories of both life sciences and healthcare converge towards a common goal of predictive, preventive, personalized, and participatory healthcare. In this future landscape, access and insight to data from various sources will be paramount to a knowledge-based system of pharmacovigilance. The common analytic foundation of healthcare and life science will lead toward improvements in public health and a population-based predictive pharmacovigilance model that relies on intelligent signal detection.

The Evolution of Pharmacovigilance and Safety Surveillance

The detection, assessment, understanding, and prevention of adverse events (AEs) of medicines, in other words pharmacovigilance, are all an integral part of clinical research, pre- and post-approval. Good pharmacovigilance, underpinned by the science of clinical pharmacology, is crucial throughout the product life-cycle. A number of recent high-profile drug withdrawals has highlighted the strengths and weaknesses of the current systems and has provided a good indication of how much more needs to be done. Significant harm, to even a few patients, can have catastrophic ramifications including a loss of trust and credibility for the pharmaceutical industry and regulatory agencies. At a time when the industry as a whole is undergoing tremendous pressure on productivity and revenues the importance of effective pharmacovigilance is even more evident.

Over the past two decades, pharmacovigilance has undergone an evolutionary shift from limited systems that mainly focused on regulatory compliance to the richer, more sophisticated systems currently in place today. In the 1980s systems were based on processes owned by biopharmaceutical sponsors, with data inputs coming in from a limited number of data sources (i.e. consumer/healthcare professionals and via clinical trials). These systems were built around case processing with limited focus on intelligent information consumption and benefit-risk analysis. It was very much a reactive, event-driven process. During the following decade, the focus shifted to improving the flow of information.

Additionally, the drug-safety environment became progressively more risk-averse, with regulators introducing increasingly stringent regulatory requirements. This saw the implementation of a regulatory framework that promoted well-structured and expeditious information flow. Although adverse event reporting has always been mandatory for pharmaceutical companies, on the healthcare side adverse event reporting was, and still remains, voluntary.

From the mid-to-late 1990s, as reporting became ‘routine’, there was a realization that there needed to be an expansion beyond the limited data sources. The arrival of the new millennium also saw another significant shift, with the move towards an environment that focused on gaining a greater understanding of the data. Risk management activities came to the fore as the pharmaceutical industry and regulators expanded the focus of good pharmacovigilance—beyond data collection to drug safety surveillance models that had more inherent value (see Figure 1).

Focus on Risk Management—The Drug Safety Model

The evolution of pharmacovigilance and safety surveillance, from yesterday’s focus on transactional activities and information flow to today’s awareness of the importance of risk management, led to the introduction of the Risk Management Plan (RMP) in Europe in 2005. The RMP is a mandatory requirement for marketing authorization applications (MAAs) for new chemical entities, biotechnology products, new routes of administration, new dosage forms, new

indicators, and new patient populations. The US equivalent, a Risk Evaluation and Mitigation Strategy (REMS), is not a statutory requirement unless the US Food and Drug Administration (FDA) specifically requests its inclusion in certain drug applications.

Risk management and rigorous adherence to drug safety has always been an intrinsic part of the drug development process. Nonetheless, the approach to risk management activities has seen a significant change as processes become more standardized, driven by the new regulatory requirements. The need for greater accountability and continuous improvements in identifying and communicating the benefit-risk associated with a drug has led to more-comprehensive, formalized processes that support REMS/RMP requirements. Formalized processes also help better define and identify the information and technologies needed to facilitate better decision making around risk management. Thus, the next step is to develop an understanding of the safety profile of a medicine through access to additional, richer sources of data. Although the traditional data sources—safety data from clinical trials and voluntary reporting of spontaneous adverse events (SAEs)—continue to provide essential information for conducting pharmacovigilance, it is well recognized that they have their limitations. In the digital era the increasing availability of large collections of electronic data from the healthcare environment, in the form of electronic health records (EHRs), insurance claims databases, outpatient data, a variety of longitudinal observational data sources, and clinical trial registries, provides alternative sources of data that could be used to gain valuable insight about the behavior of the approved product and to support pharmacovigilance processes. This has led to a growing interest in how to leverage these rich data sources to improve safety signal detection and risk management strategies.

Knowledge-based Pharmacovigilance
The science of pharmacovigilance is a continuously evolving discipline. As previously mentioned, the traditional data sources that the pharmaceutical companies rely on for conducting pharmacovigilance has limitations. Pre-approval clinical trials cannot capture all AEs causally related to the drug, are only conducted in relatively small patient populations, and do not adequately assess the risks of long-term exposure to the drug. The responsibility of post-approval reporting of SAEs lies primarily with the drug manufacturer or marketing license holder. However, post-approval surveillance activities are passive processes and rely heavily on the voluntary participation of physicians and patient groups. Knowledge-based pharmacovigilance integrates active AE surveillance methods using rich data sources from the public and private sectors. The evolutionary curve of technology invites change. The pharmaceutical industry, the healthcare sector, and regulators have all embraced information technology (IT) as a tool to support better processes. As digitization of healthcare data becomes routine the pharmaceutical industry and regulators are increasingly looking at all of those sources of information as potential sources of data (see Figure 2). However, while there is increasing acceptance that digital capabilities have created more opportunities to improve drug safety, there is great variability among stakeholders about how to best leverage healthcare data sources to improve safety and, ultimately, improve outcomes for patients.

Next Generation Signal Detection
The execution of knowledge-based pharmacovigilance will require robust data mining and analytical tools. The long-term vision is to leverage data sources to facilitate more-intelligent signal detection activities. This is where the promise of integrated analytic engines that apply the appropriate methodologies to the appropriate dataset has tremendous potential.

The incredible variety of data sources available will provide not only potential benefits but also specific challenges. In this vast environment of data it would be easy not to see the forest from the trees. To ensure that the benefits of these data sources are correctly leveraged it will be necessary to interrogate the datasets with the appropriate analytical methodologies.

Classical signal detection is driven by incidence counts of AEs and is retrospective and not truly predictive. The vision is to utilize the vast sets of medical data to proactively identify and manage emerging safety signals. Embedding analytic engines into core processes can help stakeholders adopt an analytical orientation and enable speed and quality of insights for complex analyses and reporting. The use of powerful analytic engines will enable a real-time, auditable means for automated signal detection. This scenario will also offer real-time analysis, documentation, and communication to provide a proactive approach to pharmacovigilance.

Review

The Future Landscape—Secure, Safe, and Harmonious

Central to many of the concepts and concepts discussed in this paper is the trajectory of the life sciences and healthcare sectors. Each sector is converging on a common goal of predictive, preventive, personalized, and participatory healthcare (see Figure 3). So what does this mean for pharmacovigilance? The increasing importance of healthcare data as an alternative and complementary data source has already been discussed. The convergence of the two sectors and the common analytic foundation of healthcare and life sciences will lead toward improvements in public health and population-based pharmacovigilance.

The intersection of the two fields starts with pharmacovigilance on the life sciences side and safety at point-of-care on the healthcare side (see Figure 3). Thus, pharmacovigilance and safety is the first and most active step in a move toward personalized health.

The next evolutionary step in pharmacovigilance will be a future where a collaborative environment creates and supports a continuous knowledge-based feedback loop; data are processed with various analytics engines; and data are presented through dashboards to generate knowledge—this knowledge is the data that are fed back into the continuous feedback cycle.

One of the driving forces for this change is the real need for the pharmaceutical industry to transform from a fully integrated pharmaceutical company business model to a networked model that derives innovation from value-added partners. Cost pressures and innovation shortfalls have forced this move toward a networked...
environment. Leading companies are having to ask the questions: what activities are core to the company and what are not? In order to achieve a networked healthcare and life sciences industry model, however, necessary transformations to the traditional clinical development paradigm must take place. Sponsors will need to embrace a network of partners—from hospitals and doctors to clinical research organizations (CROs), academia, technology providers, and manufacturing companies. Some of the practical steps that still need to be accomplished include the need for transparent data flows across healthcare and life sciences; defining common terminologies; correlating standards and data sources; establishing best practices; and, most importantly, the increasing focus of healthcare on implementing an EHR-based infrastructure (see Table 1).

The impact of the changing model on the safety side will include better practices and improved data collection. The pharmaceutical industry has been outsourcing to CROs for many years, but mainly for the purpose of clinical trial execution and rarely for safety services. More recently, this trend has been reversed and the industry has seen a dramatic rise in safety service offerings from CROs. This situation has arisen, in part, because of the rationalization of core business activities by pharmaceutical companies. It can be argued that many data collections and data processing activities are not core activities but are transactional. Thus, it is a commodity that can be performed by a service company with the right competencies better, faster, and cheaper. This enables the pharmaceutical company to focus on the analysis and examination of the data; the complex computations that give meaning to the data; and to provide valuable insights that help to improve the lifecycle management of the product.

So what will the next generation pharmacovigilance model look like? The answer(s) may come from other industries. Other industries have successfully utilized a networked, collaborative model to stimulate innovation and improve safety. An excellent example is the aerospace industry, more specifically Boeing, which has rapidly shifted to embrace a ‘network’ of partners from across the globe to develop the Boeing 787. In the banking sector technology has been embraced to provide real-time monitoring and analysis of transactions. The question is whether there are use cases for utilizing similar technologies in the life sciences and healthcare environments to transform pharmacovigilance from today’s fragmented, inefficient, and heterogeneous environment to a landscape that is simplified, standardized, and less fragmented.

The same mathematical foundations that are utilized by banks to identify fraud are being used in use cases and pilots to mine AE data for safety signals. A significant challenge is that financial data capture a vast amount of real-time results, whereas in healthcare and life sciences less real-time data are captured.

**Proactive, Predictive Pharmacovigilance**

Pharmacovigilance is still very observational. We see what happens and react to analyze why the event occurs and how to mitigate the risks. The other dimension is to be predictive. Imagine a scenario where a global safety database points patients, healthcare professionals, researchers, and safety professionals to populate the environment with safety data, minimizing the need for sponsors to collect and report that data, and to focus their resources in consuming that data for pharmacovigilance purposes. Imagine a scenario where ambulatory data, captured in real-time at a national or regional level, is accessible and associated with pharmacogenomic and outpatient data that would allow more-intelligent analysis of the pharmacological effects supported by the patient’s compliance on its therapy. This is pharmacovigilance for the future, based on a distributed Complex Event Process (CEP) (see Figure 4).

Many of the basic components required to enable this future scenario are in place or being implemented. The technology-driven transformation of pharmacovigilance is being championed by regulators and the pharmaceutical industry alike. In the healthcare sector the switch from a paper system to electronic records is in perfect alignment with the driving forces from life sciences. In an increasingly demanding and risk-averse environment innovative technological solutions will help to address safety concerns and improve patient confidence and outcomes. There are many challenges along this roadmap toward proactive, predictive pharmacovigilance but the end goal will see greatly reduced risks and improved responses to better protected patients.

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**Table 1: Opportunities for Alignment Between Healthcare and Life Sciences**

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<tr>
<th>Opportunity</th>
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<tbody>
<tr>
<td>1. Requires transparent data flows across health sciences</td>
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<td>2. Common terminologies must be defined</td>
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<td>3. Standards must be able to correlate data sources</td>
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<td>4. Best practices can be established</td>
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<tr>
<td>5. Healthcare must focus on implementing (EHR) infrastructure first!</td>
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**Figure 4: The Next Generation Pharmacovigilance Model**