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PHARMACOVIGILANCE IN A BOX

Evolution of Pharmacovigilance

Over the years the role of Pharmacovigilance or Product Vigilance (PV) has changed from capturing and reporting adverse events to a business imperative responsible for risk assessment, risk management and risk mitigation.

Drug Safety cases such as Vioxx and Avandia and product quality and manufacturing failures have increased the focus on drug safety over the last decade. With the ever rising regulatory compliance complexity and requirements, it has become a mandate to have proactive risk management strategies implemented in the early stages of drug development along with post-marketing surveillance. Thus the volume and complexity of drug safety data that is captured, processed, analyzed and reported has grown substantially.

Of the 617 new drugs approved by the US FDA since 1980, 18 had been withdrawn for safety reasons by 2003[1]. Withdrawal of Vioxx in 2004 intensified concerns about drug safety and hence also intensified efforts to improve drug safety of marketed products. The Institute of Medicines (IOM) report in 2006 and European Medicine Evaluation Agency's (EMEA's) initiative in 2005 led to the creation of the strategy document of the EMEA Road Map to 2010 which resulted in the issuance of several guidelines and regulations. These safety regulations seek to establish greater balance between pre- and post-approval risk-benefit management, thus emphasizing the lifecycle approach to drug evaluation. The FDA Amendments Act of 2007 included Enhanced Authorities regarding post marketing safety of drugs through post marketing studies and

surveillance, safety label changes, Risk Evaluation and Mitigation Strategies (REMS) etc. The FDA final rule and draft guidance of 2010 on IND Pre-marketing Safety Reporting and its two draft guidelines in 2011 related to pharmacoepidemiology studies, Electronic Health Records (EHR) and Medication Guides further solidified the safety mandate. The EU PV legislation of 2010 had several clauses with an applicability date of July 2012 which were targeted towards strengthening companies' PV systems and defining clear roles and responsibilities across both the regulatory agencies and the industry.

In addition to heightened expectations around regulatory compliance inclusive of PV systems for spontaneous reporting for marketed products and strict adherence to reporting timelines, active post-marketing surveillance by companies and the role of observational research in post marketing risk assessment (including data sources such as EHR, social media, patient registries and planned observational and epidemiology studies) requires management of large volumes of safety data from disparate sources. While sources of safety data for biopharmaceutical products have increased, evolving regulations around safety of other products such as consumer healthcare products has further expanded the scope and span of product safety data. For example, reporting of cosmetic products is mandatory in EU from July 2013. Yet another trend on the commercial side has also brought more companies and products under the ambit of safety regulations. Manufacturing and marketing alliances between large global healthcare companies and manufacturers from emerging nations such as India and China require generic manufacturing companies to establish PV systems as part of the Safety Data Exchange Agreements[2] (SDEAs).

All of the above developments have resulted in an acute need for companies to optimize their PV systems and processes. Adverse event reporting systems, databases and reporting software have evolved to allow organizations to have a comprehensive, meaningful view of the safety profile of the drug.

An essential element of defining and implementing best practices in the area of patient safety and regulatory compliance strategy is the fine interplay between domain knowledge, streamlined processes and technology innovation.

One of the means of addressing these challenges have been to outsource safety operations to specialized providers who have the required scientific expertise as well as operational excellence to provide effective and cost-optimized solutions in a globally distributed model. Outsourcing models vary by company. Some outsource the end-to-end process, some outsource select steps of the process, some require service providers to work with the company's systems and processes while in other cases the providers use their own systems. Whichever is the model of choice, the operational complexity increases with the inclusion of multiple groups and handoffs.

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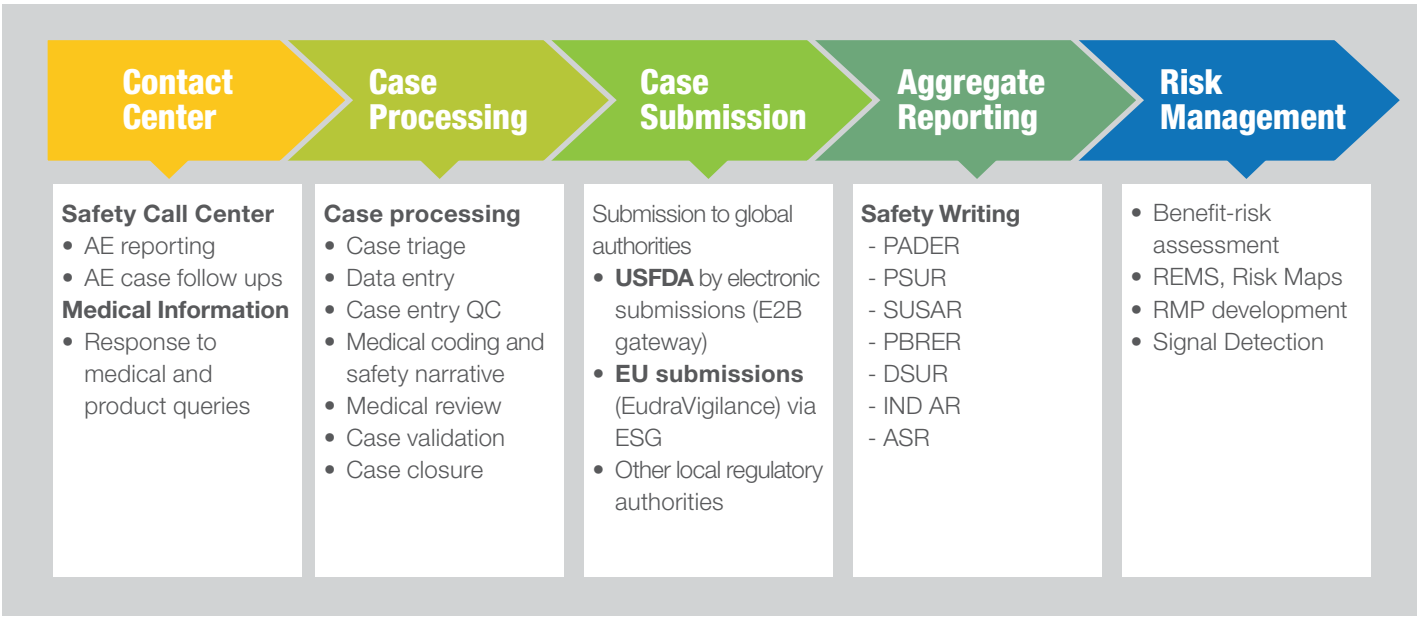
The Interdependent Safety and Risk Management Process

General Safety and Risk Management Process



The evolution of the safety and risk management process accommodates multiple models of operations such as outsourcing of sub-processes, and multiple stakeholders across different geographies. As a result, the quality of a process and thus compliance to the regulatory requirements are heavily influenced by the availability of resources and the systems that assist in the management of these resources. While quality controls are enforced through independent teams, making submissions of Individual Case Safety Reports (ICSRs) and other related documents to the regulatory agency on time require collaboration of multiple resources across time zones. All handoffs increase complexity, cost and effort. In spite of technology being an integral part of pharmacovigilance, there are multiple challenges that need to be addressed to optimize along the dimensions of effort, time, quality, compliance and cost.

The core challenge, in the ever evolving process, is adapting to the changing regulatory requirements and adhering to them diligently. Being able to adapt fast with respect to proactive patient safety and regulatory compliance necessitates efficiency and scalability in operations and consistency in quality. Sub-processes like assessment of adverse events in terms of seriousness, causality and reportability can be time consuming and unpredictable case volumes or sudden spurts in ICSRs can be difficult to manage. Moreover, parallel routing and reporting of adverse events to all internal and external recipients to ensure timely compliance with multiple regulatory requirements, locally and globally, increases complexity to the next level.

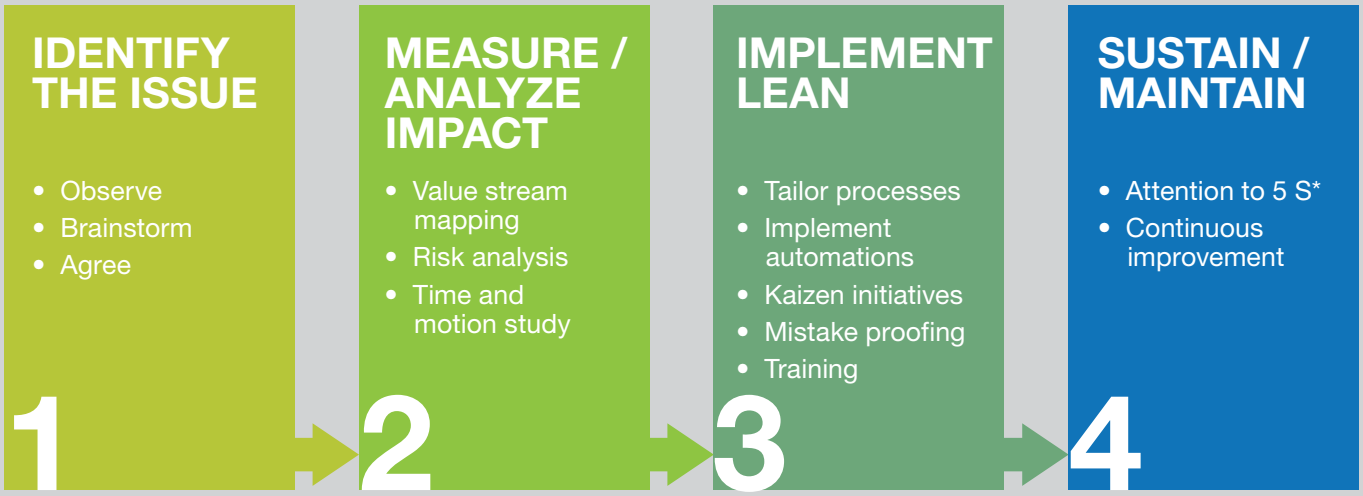
Meeting the Challenges – the Sciformix Solution

Whilst the general PV practices stay regulated, as mentioned above, methods of implementation differ across organizations. Organizational procedures are derived from its technological alliances, geographical footprint, product line and regulatory jurisdictions.

For instance, the approach and conventions for a PV process may differ based on the choice of commercial database, associated safety technologies adopted, reliance on legacy systems and handoffs across different teams.

In our experience while working with clients, we've observed that these multitudes of variables introduce inherent loops of redundant sub-processes that often cause delays or deficient case quality. While it might never be possible to do away with the variability, we can help organizations effectively manage it. By adapting a client's processes and standardizing their sub-processes through a LEAN paradigm and by creating an automation layer that seamlessly traverses the information silos we can ensure compliance while optimizing requirements of all types of resources. By making the process nimble, we can focus on producing homogenous results which conform to compliance and quality under different environments.

LEAN Implementation Process



**Seiri, Seiton, Seiso, Seiketsu, and Shitsuke* : Sort, Straigten, Sweep, Standardize & Sustain

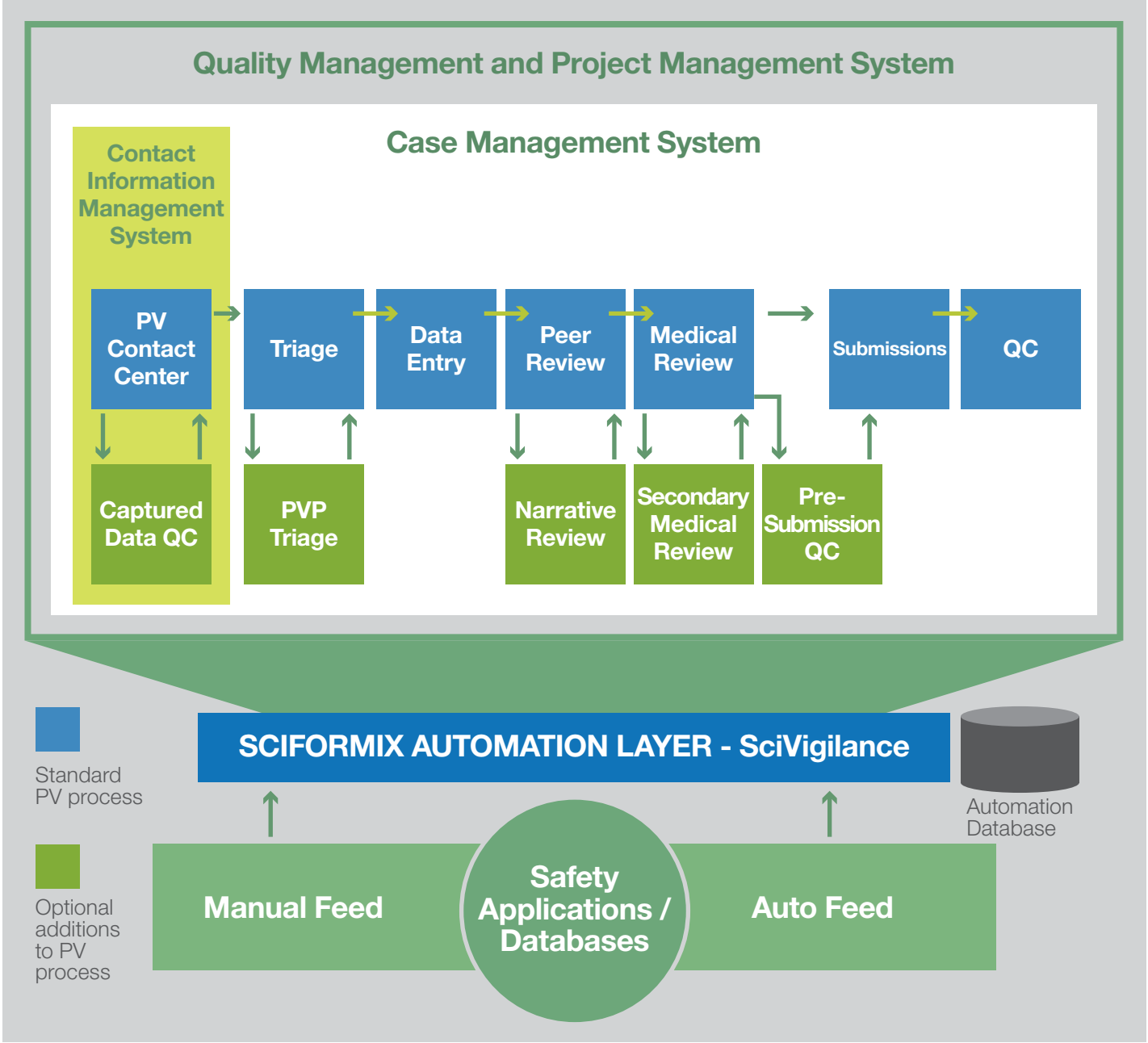
An illustrative example of implementation of the LEAN paradigm and the reduction in number of process blocks and cycle time is described below.

Sample Performance Through LEAN

Process Step	Measure	Current	After LEAN & Automation
Pre-Triage	Count of Process Blocks	16	2
	Cycle Time	45 minutes	~7 minutes
Case-Processing (DE)	Process Blocks	06	06
	Cycle Time	25 minutes	~15 minutes

Furthermore, we have developed an overarching automation layer which can be easily applied to any PV process of any client. We realized at the outset that such automation encapsulating PV operations would have to work without any changes of codes in the underlying call center, case processing and allied systems already in use and minimalistic changes to the operational SOP's. Thus we built an agnostic system based on robust technology with a three tier architecture that is highly configurable and customizable and enables LEAN processes to be implemented without changing the code base. We call our automation layer SciVigilance. SciVigilance allows the client to continue working seamlessly across multiple underlying safety applications (databases and tools).

SciVigilance - Base Architecture



The automation layer integrates proactive case management, quality management and project management of PV process into a compliant and structurally validated system with inherent traceability and audit trail. The bi-directional data flow between underlying systems and the automation layer minimizes process time by traversing process blocks and synchronizing data. It increases effective case management through active tracking, strategic alerts and notifications that allows personnel to focus on core business objectives.

Conclusion

Effective safety and risk management is a result of a multi-tiered effort from all stakeholders - sponsors, payers, health personnel and patients, to ensure safety of the products for patients and to mitigate financial risk for the company. Pharmacovigilance requires informed decisions regarding the safety and risk of the product while meeting targets of quality, time and cost.

Our experience demonstrates that agile processes and robust technologies provide vital scientific insights, process visibility and key trends for the leaders to make real-time and proactive decisions.

While pharmacovigilance depends extensively on human sources for information input and processing of data, the growing volume of data and evolving regulations necessitates robust technology enabled process execution to manage the myriad of risks. Streamlined and agile processes ensure consistent quality, improved efficiencies, adherence to timelines and regulatory compliance. The synergistic combination of process expertise and domain knowledge facilitates swift and effective decisions in all stages of the product life cycle.

Technology and process enhancements play a crucial role in effective management of pharmacovigilance. Technology fosters collaboration between disparate teams, enables seamless flow of data, streamline capture, processing and analysis of data. Cumulatively, effective combination of domain expertise, agile process and robust technology has allowed us to consistently demonstrate time savings, high quality, cost reductions, increased efficiency and absolute compliance. At the project level, technology allows almost real-time tracking of risk-benefit profile and helps in informed decisions on risk minimization much faster, ultimately leading to safer and efficacious medicines.

References

1) A) The Medical and Healthcare Marketplace Guide, 19th edition. New pharmaceutical products in the United States. Dorland Healthcare Information 2004.

B) Tufts Center for the Study of Drug Development Impact Report. Drug Safety Withdrawals in the US not linked to speed of FDA approval, Sep/Oct 2005.

2) Innovator Pharmaceutical and Generic Manufacturer Partnerships: A successful path to fulfilling pharmacovigilance obligations. Chitra Lele PhD, Chief Scientific Officer, Sciformix Corporation, June 2013

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