

Developing Holistic Safety Risk Management

Traditionally the approach to drug safety has been focussed on the reactive; the receipt and reporting of single spontaneous cases from post-marketing, with the clinical teams being relied upon to manage safety activities in development. Recent events have shown that this is not enough to ensure visibility of safety risks during clinical development. Dr. Mark Perrott at WCI Consulting Ltd looks at how pharma companies can develop effective lifecycle-long safety risk management.



Dr. Mark Perrott is a Managing Consultant with WCI Consulting Limited. Since joining the organisation in 2003 Mark has delivered multi-£m programmes within leading companies in both the UK and the USA. Mark's areas of expertise include: Business Process Redesign, Change Management, Programme and Project Management and Relationship Management. Mark has a PhD in Physiology from the University of Manchester and a BSc. (Hons) in Marine Biology from the University of Liverpool.

Life Science companies have public responsibilities beyond those of ordinary business ethics. Public safety is paramount and, in the context of drug development, it is important to make all reasonable efforts to understand the emerging benefit and risk profile of a product. This will not only ensure that the patients entering trials are protected, but that the risk of product failure is appropriately managed. Recent drug withdrawals and failures to obtain approval have put both industry and regulators under pressure to improve safety surveillance during drug development. This has led to pressures to bring the safety risk management processes of Pharmacovigilance into earlier phases of development, thus making Pharmacovigilance increasingly business critical.

Traditionally the approach to drug safety in clinical trials has been based on the end of study analysis of individual trial data, with adjustments being made to risk and benefit statements in the investigators brochure which would then go on to be the safety benchmark for subsequent trials and form the basis of the final Core Safety Information. This approach is no longer enough. In an environment where many companies have yet to establish robust systems for post marketing signal detection and management there is a clear and increasing need to use Pharmacovigilance approaches to look for safety signals during clinical trials. If you don't, or don't do it correctly, then someone else will. When Bristol-Myers Squibb and Merck had a positive Advisory Committee hearing for their dual PPAR agonist Muraglitazar they could not have realised that a meta-analysis of their trials by an independent group of medical academics would have highlighted safety concerns that led to its failure to reach the market.

Clinical trial safety data are more complete than post-marketing and spontaneous data, but challenges do exist in detecting safety signals therein. Trials tend to be powered on efficacy, rarely by safety, with relatively low numbers of patients actually exposed to drugs during a trial programme, typically a few thousand. This makes the ability to detect rare events something of a challenge. In addition, safety endpoints are variable and usually exist in the form of laboratory



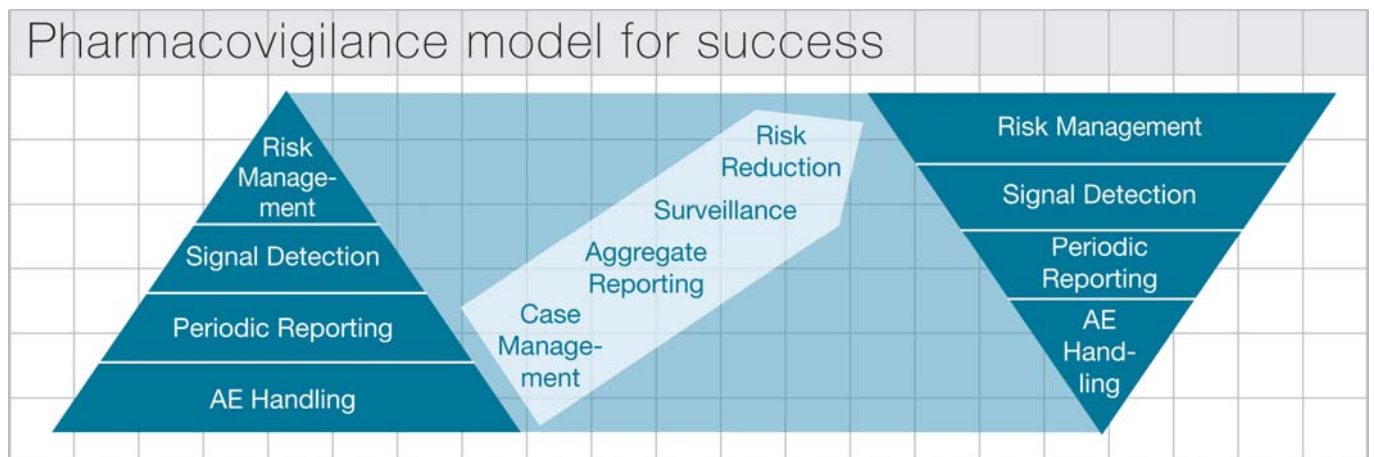
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data and adverse events. Reporting bias exists with regard to adverse events, there are coding issues, different thresholds for reporting by different reporters and the problem of adverse event data often being heterogeneous. These issues, coupled with a lack of robust signal detection processes and technology, can result in signals going undetected or being regarded as insignificant.

So what is the industry doing in an effort to identify safety signals, either in post marketing or during clinical development? There is an expectation that companies will put structures and methods in place that are capable of detecting safety risks across the product life-cycle, and to implement measures to mitigate and manage any newly identified risks. A recent survey of the top 20 pharma companies confirms that the majority of companies are reviewing their methods or plan to take new approaches to Safety Risk Management. Increasingly, Pharmacovigilance is being seen as the function with the responsibility to ensure the safety and well being of trial subjects and patients through the complete life cycle of the product. To this effect, pharmacovigilance responsibilities are shifting from being a primarily regulatory compliance-oriented function, to being a proactive strategic and analytical function, taking into account safety aspects in a holistic and integrated way and co-ordinating safety related cross-functional activities. As Figure 1.0 demonstrates; drug safety processes are evolving to meet the new challenge. In such a highly regulated and constantly changing environment it is obligatory to take a proactive approach and invert the triangle.

Figure 1.0



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In order for companies to ensure that they have visibility of safety risks during development and beyond, it is essential to create equilibrium across people, processes and technology. This in itself poses challenges:

People

The pharmacovigilance organisation must be aligned to support signal detection. A formalised safety culture in Development is a new concept for many companies, but to meet the new challenges; roles and responsibilities for safety monitoring and governance must be established.

Key safety risk managers need the right skills balance, a balance that largely does not exist at the present time as needs for new or stronger skills are emerging:

- deep knowledge of early-phase processes and tools;
 - understanding of risk and risk management planning;
 - data mining and aggregate data analysis;
 - knowledge of products and therapeutic area populations;
- and
- leadership skills to be effective participants in the development process

The pharmacovigilance safety risk management experts need to work together with their colleagues across the business, and especially in the Clinical arena, to develop new ways to lead safety assessments. Effective companies are employing comprehensive change management strategies to strengthen buy-in with Therapeutic Areas:

- Strong, frequently-communicated business case for the change in the role of PV in development
- Developing in-house fellowship programs to accelerate learning and growth for key individuals
- Engaging experts from relevant outside disciplines (epidemiology, biostatistics, etc.) to support the PV Team in its signal detection and safety risk management activities

Process

Processes must reflect the different needs of development and post marketing while making best use of established safety risk governance structures such as the CIOMS recommended Safety Management Team and Executive Safety Decision Board. Processes must support the analysis of early clinical data (often blinded) in ways in which it has not been looked at before. Associated challenges include:

- Limited understanding of early phase processes and tools
- Establishing and maintaining credibility within clinical organisations in the face of potential resistance to this new role for pharmacovigilance



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- Developing 'surveillance engines' – high through-put, rapid-review signal detection and management systems and processes to facilitate the availability of and access to up-to-date safety profiles
- Strengthening understanding of external databases and the opportunities and challenges of pharmacoepidemiology

Technology

For the most part, clinical data is in clinical databases rather than safety databases. Tools must be available to enable the early identification of trends and signals in small volumes of data. As safety and risk management processes are being extended earlier into Development phases there is a growing need for information systems to facilitate the aggregation and analysis of data across the Development lifecycle.

Companies are investing in tools to support proactive pharmacovigilance. Systems that capture and track clinical trial information are typically not integrated with Safety Databases, and processes to include SAE information from clinical trials are largely manual. As a result, systems are not in place that afford a complete view of a product's history and safety profile from development through to post-marketing

Safety Risk Management, Epidemiology, and Medical Assessment and Benchmark

Commissioned in January 2006, WCI Consulting Limited carried out a 'Safety Risk Management, Epidemiology, and Medical Assessment Benchmark' at twelve of the world's leading pharmaceutical and biotechnology companies. The survey participants included senior pharmacovigilance experts including Heads of PV, PV IT Leads and PV Business Leads.

A Summary of Key Findings

Of those surveyed:

- 100% confirmed having drug safety/pharmacovigilance departments involved in initiating and leading Safety Risk Management Activities
- 50% start formal Safety Risk Management planning activities before Phase II/III of the product lifecycle
- 50% have a Safety Risk Management Standard Operating Procedure
- 58% have a formal process for RiskMAP preparation
- 67% have a cross-functional Safety Management Team in line with CIOMS VI recommendations
- 42% have a Standard Operating Procedure covering roles and responsibilities of Safety Management Team members
- 58% have an Executive Safety Decision Board to which Safety recommendations are elevated
- 67% have Epidemiologists as ad hoc members of clinical project teams
- 58% have a drug safety/pharmacovigilance epidemiology group performing safety related epidemiological activities



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Conclusion

Even in the world's largest Pharmaceutical companies, processes and supporting organisations and technology for signal detection and management are not universally in place even for marketed products. Developing holistic safety risk management is of key importance to the success of current Pharmaceutical organisations. The result? A safer environment and a proven structure for managing risk that proves to the regulators and shareholders alike that you are practising proactive pharmacovigilance. As with many areas within the life science industry, there are substantial challenges. Some organisations are already facing these challenges but few are taking the necessary big strides. All will need to follow suit, sooner rather than later, if they are to successfully compete in this ever changing regulated environment.

Mark will be speaking at the DIA Annual Meeting 2007 at a session titled 'Detecting Safety Signals in Clinical Trials' chaired by Stephen Buckley, Director Safety Evaluation Risk Management, GSK.



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