

**LIFE SCIENCES**

Pharmacovigilance

Drug safety  
Safety risk management  
Regulatory compliance  
Drug development

tide of  
change in  
drug safety

why



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define the future  
of drug safety ”**

**Why this is important**

There is a tide of change in drug safety within the pharmaceutical industry. Internal and external forces are pushing drug safety to expand its scope of operations; from post marketing safety monitoring to a much more active stance in the characterisation of safety profiles during the development of new drugs. Taking drug safety operations from the reactive approach that dominates the industry to an approach that is more proactive will result in greater safety input during drug development. This has to be the right direction as drugs are now omnipresent in all facets of our lives. However, this does call for a huge cultural and technology shift in the world of drug development.

**Tightening regulation**

Highly public drugs failures, such as Vioxx® in September 2004; the largest prescription drug withdrawal in history, have led to pharmaceutical companies being under even closer scrutiny from regulators and the media alike. All too frequently are companies being accused of putting profits ahead of patient safety and the number of stories in the mass media is on the increase all adding to growing public anxiety. The climate of heightened concern for drug risk, with relatively little debate or public education on the concept of benefit/risk balance, has pushed legislators and regulators into an increasingly risk-averse stance. For example, in the EU, regulators now require new drug submissions to be accompanied by a formal statement of the need (or lack of need) for a risk management plan, and the need for global consistency is resulting in submission of similar documentation wherever a drug is to be launched.

In the Food and Drug Administration Amendments Act of 2007<sup>1</sup>, which was recently passed by the House of Representatives, there are clauses which describe the requirements for publication

of both development and post marketing clinical trial results. This proposed new legislation also highlights the development of safety signal monitoring processes by the FDA and describes the tightening of enforcement actions if companies do not follow their own risk management plans.

It is very clear that where there are outstanding questions from the drugs development phase in relation to defined patient populations the drug's developer must describe the actions to be taken to close these knowledge gaps. For example; if there are gaps in the understanding of the benefit/risk ratio and the adverse event profile, in relation to that of the likely real-world patient population, actions must be described to fill the gaps. The EU has defined the specifics of this in great detail in the template documentation that is provided. These actions can range from typical post marketing safety monitoring through to the initiation of targeted clinical or epidemiologic studies of safety, which may be accompanied by restrictions on the use of the product until that information is obtained.

Where such activities are committed to at submission, the company will need to ensure the appropriate mechanisms are in place across clinical, safety, regulatory and the marketing and sales organisations to guarantee that the actions are taken and, importantly, that they are effective in the control of risk.

Traditionally the industry answer to the need for drug safety has been ‘pharmacovigilance’. This is particularly concerned with both monitoring and reacting to Adverse Drug Reactions (ADRs), but it often only covers the post marketing phase of drug development. Agreeably a step in the right direction but, in reality, a sticking plaster over what can only be described as a fast growing issue. As the public and regulatory focus on

safety grows, pharmaceutical companies need to find ways to ensure that the benefit and risk profiles of their products are fully understood throughout development, and are transmitted effectively to customers as the products reach the marketplace.

The pressures on the industry are, therefore, two-fold:

1. To reduce complex and expensive post marketing commitments and product usage restrictions as much as possible. This is achieved through understanding the safety profile of any new drug in development as accurately as possible and to answer as many of the key regulatory areas of concern prior to submission
2. To develop the cross functional mechanisms which will enable the development of appropriate, effective and ‘implementable’ Risk Management (or Minimisation) Plans, coupled with the monitoring mechanisms and governance processes to ensure that they are effective.

**Development Safety Risk Management**

All stakeholders are concerned with how to identify Adverse Drug Reactions (ADRs) earlier in the product lifecycle to ensure that better decisions can be taken on their mitigation before the product reaches the marketplace, and rightly so. To achieve this, safety monitoring during drug development must be less reactive and more proactive. In short, this means that clinical and drug safety must work in tandem, rather than as two distant functions responsible separately for product development and marketplace monitoring. It is no longer enough to report development safety events in a timely manner. Now you must both anticipate and mitigate safety risk. The price to pay for non-compliance is high – warning letters that risk the global reputation of

<sup>1</sup>An act to amend the Federal Food, Drug and Cosmetic Act to revise and extend the user-fee programmes for prescription drugs and medical devices, to enhance the post market authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes

**“we balance performance and compliance, enabling our clients to be more effective and efficient in drug safety”**

the company, new legislation enabling regulators to levy huge fines, and product withdrawal which can cost an organisation millions and put jobs at risk.

The nub is that clinicians and drug safety work independently, almost as two separate business units or entities. Even during the clinical trial phase, product safety is still reviewed in silos. With different groups looking at risk at various stages of the product life cycle; limited consistency of the approach, coupled with safety reviews of separate clinical trials, rather than across all available data could mean that links which highlight an ADR are missed at the early stages and, if you don't think that risk exists, you cannot put the actions in place to manage it. With this in mind, it is imperative that the industry makes a huge shift in its approach. Clinical and Drug Safety experts bring two very different, but equally valuable, perspectives and need to work together as peers to describe the benefit and risk balance for a product ahead of marketplace release. It is important that formal accountabilities are separated; however, the sharing of knowledge, data and expertise should be a prerequisite. It is widely accepted that the key driver for product progression in Research and Development is the risk/benefit balance. In working independently, risks can be an increased problem. For example, there may be a delay to regulatory approval, pending further safety studies that were not carried out during initial trials, yet this risk of delay could be managed, or avoided, should experts work effectively together. The industry needs to work towards changing the perspective that drug safety is something which happens after launch.

Leading edge companies are beginning to establish the mechanisms to achieve this new outlook. Cross functional safety

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management teams are being put in place to work alongside the clinical development teams. These new teams have a clear focus on building a companies understanding of the emerging safety profile of products in development using all available data to build this picture. This data may include pre-clinical studies, external databases of patient information or information on similar products that are already on the market. Whatever the source of information, these new teams are responsible for developing a view of the product's likely safety profile and pro-actively testing their models through the development process to continually refine their understanding of the emerging safety profile. This information is then fed into the broader development process, ensuring that the clinical and pre-clinical studies address the need for information on the safety of the product in the most appropriate way.

To achieve this, drug safety needs to recruit personnel who can work effectively peer-to-peer with the senior doctors that run Clinical Development. The right people are needed to lead the change from a reactive to a proactive stance. This requires a whole new skill set in tomorrow's world and a major shift in the relationship between Drug Safety and Clinical, to redefine the status of Drug Safety and build career pathways that enable highly skilled scientists and clinicians to move between these partner departments.

Beyond the cultural hurdles, technology is also a huge mountain to move. In order to use clinical data as part of early drug safety signal detection, it must be collated, formatted and analysed differently. Clinical trials are powered to detect efficacy not safety and so analyses need to make the best use of all available data, using meta analysis across multiple trials, so as to

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spot safety trends throughout the clinical trial process. This brings challenges both within companies that manage their own clinical and safety databases, and in the relationships between companies and their CRO suppliers who will need to be able to provide their sponsors with not only an end of study report, but also a consistently formatted dataset for further analysis.

All of this activity must result in a more consistent view of the safety profile of a development product, but it must also lead the company to a way that ensures that the safety risk is consistently well managed. Safety risk management in development is accomplished through multiple mechanisms including the Investigators brochure, the inclusion and exclusion criteria in clinical trials, SAE reporting guidelines etc. In many cases, these safety risk management mechanisms are independent of one another, thus leading to a risk of inconsistency. Bringing the core of this safety risk management together into a development safety risk management plan with clear relationships to all of the other key safety risk management mechanisms will ensure that there is one clearly identified source of guidance. This 'living' document (which would be updated at least at each major development milestone, and which would ultimately evolve into the submission risk management plan) would give senior managers transparency of the risk management approach and greatly ease communication across all participating departments.

### **Safety Risk Management at submission and beyond**

With the regulators now demanding that a justification for the risk management approach be written, and where there are



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risk minimisation activities implemented and monitored, for every new product, there is a need to ensure that any safety risk management activities are likely to be effective and are feasible. This calls for a much greater degree of co-ordination across Safety, Clinical, Medical Affairs, Marketing and Sales departments than has been required in the past for all but the most significant of company crises.

The definition and implementation of these Safety Risk Management activities will call for highly cross functional teams, operating at a level within the organisation that they can mobilise resources across R&D and Commercial divisions. These are levels of organisational co-ordination and interdependence that have rarely been called for in normal operations and will require clarity of focus and leadership to be successful.

Where there is a need to make commitments to post marketing risk minimisation activities,

or 'enhanced PV', there is a need for careful design of the approach, taking into account the need to obtain additional safety information and the practicalities of data collection in a post marketing environment. The approaches taken may include specific studies to monitor certain safety aspects, the development of patient registries to track product usage, restrictions in supply and communication plans to support messages of appropriate product usage. Whatever the approach taken, the development of the plan and its implementation must be a cross functional activity, incorporating multiple central and affiliate functions for greatest effectiveness. The implementation must be measured to assure the company and the regulators that actions committed to are being carried out but, more than that, measures must be put in place to monitor the effectiveness of the actions. If the plan is ineffective at managing risk, it becomes a risk in itself. The most obvious candidate to lead this activity is safety, working through a mechanism like the Safety Management

Team, although now transferred into the post marketing environment, in addition, the appropriate skills will need to be developed or be put in place to carry out this new leadership role.

This is clearly an enormous challenge that supports the push for more proactivity within the industry. Whilst many companies have the corporate will, they do not necessarily have the skill set to follow through on such plans and, thus, proactively manage safety risk. The tide is most certainly changing, but progress is slow. The established relationships and profiles of the affected functions mean that 'the way we have always done it' and the lack of new skills will slow progress. The will to do this from the top must permeate effectively down to encourage massive cultural and technological change to achieve these goals, representing years of effort and many millions in investment for the entire drug development and lifecycle management chain.



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