Quanticate
The Clinical Data Experts

Prepare for the Unexpected

Quanticate discusses the current trends in pharmacovigilance, highlighting the importance of its integration throughout the entire product life cycle

Since their introduction in the wake of the Thalidomide tragedy in the 1960s, international pharmacovigilance systems have been evolving to meet the changing requirements for effective protection of public health. There has been a shift towards a more proactive approach, not only to identify and evaluate potential safety issues, but also to minimise risks and promote the safe and effective use of medicines.

There are several driving factors behind the current trends in pharmacovigilance. These include globalisation of the pharmaceutical market with extensive patient exposure over a short time period, heightening the need for effective pharmacovigilance systems to quickly detect and manage potential safety issues. Another factor is the development of innovative products with as yet unknown safety profiles, which therefore require careful monitoring – for example products based upon new technologies, such as biologics and gene therapy, as well as those products which act on novel targets or work through mechanisms of action previously untested in humans. There is also increasing public awareness and changing expectations with regards to the safety of medicines, fuelled by recent high profile safety issues and product withdrawals. Another important factor is the large costs associated with drug safety. This applies both to pharmaceutical companies looking to halt the development of products with an unacceptable risk-benefit profile as early as possible, in addition to the cost to public health, with an estimated five per cent of hospital admissions in the EU thought to be due to an adverse drug reaction (1).

The development of new and effective medicinal products makes a positive contribution to the health and well-being of individuals. However, there is a need to improve pharmacovigilance systems to more effectively monitor and take action on safety issues associated with medicines and in so doing enhance their contribution to public health. This article looks at the current trends driving the development of pharmacovigilance strategies in order to achieve this aim.

INTEGRATED PHARMACOVIGILANCE THROUGHOUT PRODUCT LIFE CYCLE

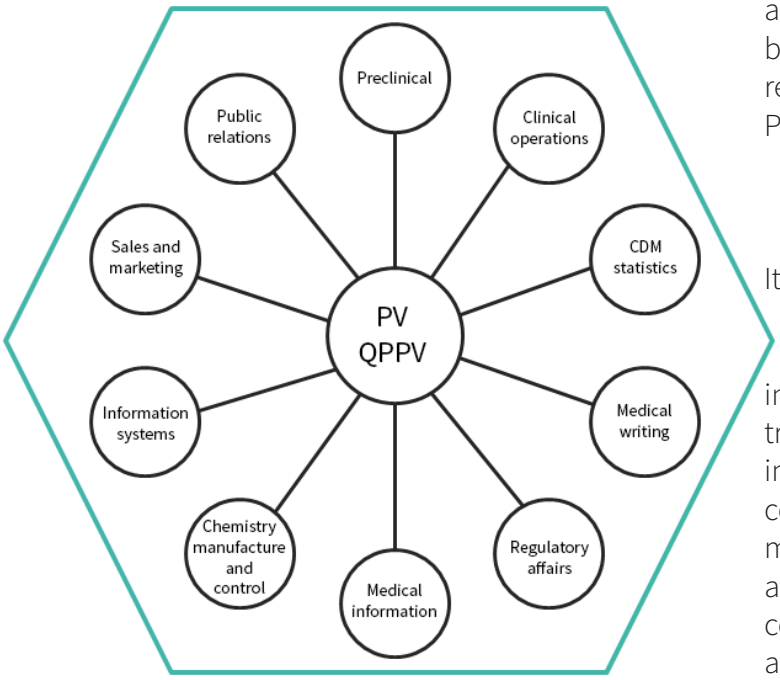
In the past, pharmacovigilance has concentrated primarily on post-marketing safety surveillance. However, there has been a shift in recent years towards systematic pharmacovigilance throughout the product life cycle, as recommended by the CIOMS V Working Group (2).

While acknowledging that the post-marketing use of products will involve the exposure of a large number of patients, and thus may demonstrate previously unseen, rarer adverse drug reactions, there is still a lot to learn about potential risks in the clinical trial stage, as well as from preclinical studies. The benefit of preparing a development risk management plan (DRMP) and evaluating clinical trial safety data on an ongoing basis is becoming more apparent and is discussed further in later sections.

To prove effective, pharmacovigilance systems need to integrate input from all stakeholders, both within an organisation and externally. The stakeholders within an organisation are many and diverse, as illustrated in Figure 1. These include the clinical operations, clinical data management (CDM) and statistics teams, with their role in running clinical trials and managing and evaluating clinical trial data.

Regulatory affairs, medical writing and public relations have a key role in the implementation of labelling updates and communication of safety information.

Figure 1: Pharmacovigilance stakeholders within a sponsor or licence holder organisation



Pharmacovigilance should be a consideration right up to board level to ensure that corporate policies and procedures facilitate the oversight and management of the safety of products and allow escalation of issues quickly and effectively if required. A further important consideration is that many of these activities may be handled by affiliate or partner companies, or outsourced to one or more CROs. These parties also require integration to provide a clearly documented, coherent, life cycle pharmacovigilance system; comprehensive safety data exchange agreements (SDEAs) can ensure this.

The Quality Assurance (QA) department also has a key role in the auditing of the entire pharmacovigilance system (including affiliate and partner companies, CROs and other third parties) to ensure that suitable processes are in place and are followed to a high standard. Lastly, oversight of the entire pharmacovigilance system is required, for example by the EU qualified person for pharmacovigilance (QPPV), for post-authorisation products. A company safety committee or similar, comprised of representatives from each function relevant to pharmacovigilance, can also be established to coordinate activities, review all necessary information and agree on actions required and their communication to relevant parties.

From the regulatory perspective, the implementation of the development safety update report (DSUR) in September 2011 has served to harmonise clinical safety reporting across international conference on harmonisation (ICH) regions, in addition to coordinating safety reporting across the product life cycle, through its overlap with the periodic safety update report (PSUR), which was also updated in January 2013, to the periodic benefit-risk evaluation report (PBRER) in the re-vamped post-authorisation Guideline on Good Pharmacovigilance Practises (GVP) Module VII .

SAFETY DATA MANAGEMENT & EVALUATION

It is a growing challenge for pharmaceutical companies to manage the large amounts of safety data from numerous sources. The volume is increasing with the conduct of more global clinical trials and post-marketing studies. This will intensify as the new guidance to strengthen consumer reporting in the EU are implemented, making it a requirement to report to the regulatory authorities adverse reactions received directly from consumers, as is already required in the US. In addition to the increased volume of case safety data that this generates, there is also the need for additional follow-up to ensure report accuracy and quality. For smaller Phase I and II studies, a paper-based system and spreadsheets may prove sufficient for safety data management. However, as the case volume increases, a validated, regulatory compliant safety database becomes a necessity.

The requirement for unblinding of suspected unexpected serious adverse reactions (SUSARs) prior to reporting to EU competent authorities and ethics committees necessitates careful planning and safety data management. To maintain the integrity of the trial, companies must decide which personnel will have access to unblinded data (such as members of the pharmacovigilance group) and who will not be permitted access (such as clinical and biostatistics personnel involved with the conduct and analysis of the trial).

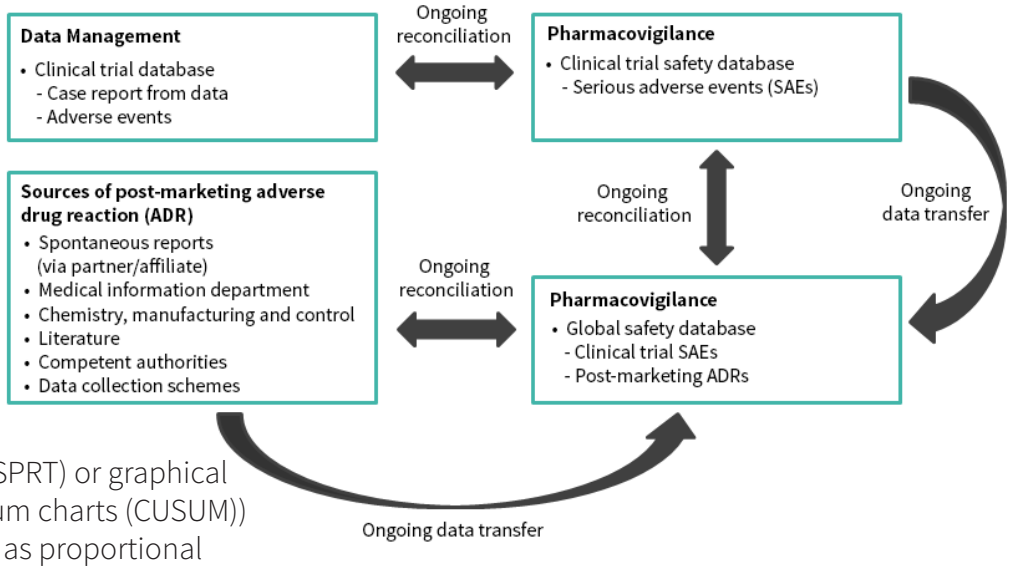
Guidance also suggests that investigators should be kept blinded, which adds to the challenge, particularly for the preparation and submission of periodic reports. Technological advancements do facilitate the management of unblinded data, with the ability to store password-protected unblinded data on the safety database. However, definition and documentation of the blinded and unblinded team and processes to maintain these are also helpful.

Sponsors and marketing authorisation holders are increasingly looking for ways to systematically review safety data and perform signal detection and evaluation on an ongoing basis. The use of data safety monitoring boards (DSMBs) for the monitoring and assessment of data during clinical trials is increasing due to its provision of unbiased review, which may be unblinded without affecting the trial integrity. One consideration is the inclusion of members with knowledge of areas associated with potential risks, in addition to the therapeutic indication of the product.

The value to the pharmacovigilance department of involving data management and statistics expertise in safety data management and evaluation is becoming apparent. Formal signal detection methodologies using statistical techniques adapted from manufacturing (such as sequential probability ratio test (SPRT) or graphical techniques such as cumulative sum charts (CUSUM)) or data mining approaches (such as proportional reporting ratio (PRR) or Bayesian confidence propagation neural network (BCPNN)) are generally applied to large post-marketing surveillance databases. The volume of safety data within a licence application may be such that a subset of such graphical or statistical techniques could be applied to support the medical review and evaluation. The long awaited CIOMS VIII guidelines on signal detection, published in 2010, have enabled some further pragmatic solutions and guidance for effective signal detection to be integrated into the recent GVP Module IX on Signal Management.

With safety data being received from numerous sources and held on different clinical and safety databases, effective data flow and reconciliation is vital to ensure the integrity of the databases (see Figure 2). This must work across all groups handling safety data, be they from within the organisation or CROs. Also, there is a requirement for integration of data for analysis and evaluation and inclusion in documents such as the integrated summary of safety (ISS) for a new drug application (NDA). This requires pooling of adverse event (AE) data across studies. Careful consideration should be given to ensure biases are not introduced by inappropriate pooling, such as different treatment regimens or differing lengths of treatment. Centralisation of case report form (CRF) and safety data provides efficiencies and facilitates a high quality global safety database.

Figure 2: Data flow and reconciliation between sources of safety data and clinical trial and safety databases



One of the more significant changes in the new post-authorisation GVP legislation is the goal to strengthen safety data collection by regulators, with the EudraVigilance database becoming the single point of receipt of individual case safety reports within the community. However, as each Member State works to ratify the new legislation, marketing authorisation holders must comply with a complicated set of transitional measures to ensure compliance in regulatory case reporting. The US FDA are also proposing to amend post-marketing safety reporting regulations to make electronic safety reporting mandatory.

TRANSPARENCY & COMMUNICATION

Public awareness and expectations with regards to the safety of products is increasing, as are the demands on companies and regulators for transparency, with effective and timely communication of drug safety issues. The aim is to enable healthcare professionals and consumers to make informed decisions about medicines prescribed and to promote the effective and safe use of those medicines.

Transparency and communication will be best served through gaining input from all external stakeholders in pharmacovigilance. Recent changes to pharmacovigilance EU legislation (Regulation 726/2004 and directive 2001/83/EC) were developed in consultation with stakeholders, including pharmaceutical companies, regulatory authorities, healthcare professionals (HCPs) and consumers. As discussed above, these changes aim to strengthen consumer reporting, which is a positive step towards involving consumers more in pharmacovigilance.

In terms of communication of safety issues and advice on the use of medicines, the proposed changes to EU legislation in GVP Module XV seek to introduce an EU web portal , which would be the main platform for announcements relating to medicinal safety and include links to member state web portals. Companies need to consider education on prescribing use, in addition to the monitoring of the use of medicines to identify any issues with the product name, labelling, packaging or use that may contribute to medication errors. Furthermore, companies require clear processes for the effective communication of changes to the risk-benefit profile of their products.

PROACTIVE RISK MANAGEMENT

The overarching trend is towards proactive risk management. Pharmacovigilance systems are therefore designed to deliver the key elements of an effective risk management system. These are risk identification and evaluation, development of risk minimisation and mitigation strategies, and the communication of those strategies to all relevant parties.

The EU regulatory changes referenced previously are designed to promote proactive risk management. Previously EU guidance suggested that a risk management plan (RMP) may be required at the time of the marketing authorisation application (MAA) if considered appropriate; however, there was no legal basis for competent authorities to request a RMP. The recent changes to EU regulations make a RMP a requirement for MAAs for all new active substances. Furthermore, EU PSURs now have a greater emphasis on risk-benefit, with the frequency of reporting being specified in the marketing authorisation (MA), dependent upon the risk-benefit profile of the medicine.

CONCLUSION

Pharmacovigilance has a vital part to play in public health. Pharmacovigilance systems must evolve to meet the changing demands and challenges to continually strive to be effective in quickly detecting and minimising risks, even for previously unexpected or inexplicable adverse drug reactions. Indeed, a primary mechanism by which Thalidomide causes birth defects was only discovered recently, nearly 50 years after the link was first made (3). Current trends see a shift towards integrated pharmacovigilance throughout the product life cycle, involving input from all stakeholders both within and external to the pharmaceutical company. Sponsors, marketing authorisation holders and regulators are endeavouring to meet the challenges posed by ongoing management and evaluation of safety data, consolidating and integrating data from different sources and carrying out systematic signal detection and evaluation. With the increasing demand for transparency, communication of potential safety issues, risk minimisation strategies and the correct prescribing and use of medicines is also important. The challenges are great and there is no quick solution, but by focusing on these key aspects, pharmacovigilance systems can be improved to allow more effective management of the risk-benefit profile of medicinal products. Achieving such systems will enable us to move closer to the ultimate shared goal of the delivery of the safest and most effective medicines possible in order to maximise their contribution to public health.

References

1. Proposal for a directive of the European Parliament and of the Council amending as regards pharmacovigilance, Directive 2001/83/EC on the community code relating to medicinal products for human use

2. CIOMS V, Current Challenges in Pharmacovigilance: Pragmatic Approaches, 2001
3. Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, Yamaguchi Y and Handa H, Identification of a Primary Target of Thalidomide Teratogenicity, Science 327(5971): pp1,345-1,350, 2010
About the authors

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