Achieving Operational Excellence in Drug Safety with an Effective Quality Management System

Abstract:
With drug safety evolving into a key priority area for the biopharmaceutical industry, the emphasis on quality and compliance has increased substantially. Regulatory agencies have made it clear that quality is integral to drug safety, and pharmacovigilance (PV) quality systems constitute the foundation of PV operations. The International Conference on Harmonisation (ICH), European Medicines Agency (EMA) and US Food and Drug Administration (US FDA) have laid out their expectations with respect to quality management systems (QMS) for PV. The past few years have also seen a steep rise in outsourcing of safety operations, (case processing, call centre, aggregate report writing, signal evaluation amongst others) and this has put the spotlight on how sponsor organisations provide oversight to outsourced operations with the ultimate goal of ensuring high quality and compliance of the deliverables.

This paper will review the QMS-related requirements and specifications, and will compare and contrast requirements by various organisations, primarily to elaborate on how these requirements can be implemented, what constitutes a robust QMS and how it can be built into PV operations. Means of ensuring quality and compliance through appropriate oversight will be discussed.

Introduction
The role of pharmacovigilance or product vigilance (PV) has changed from capturing and reporting adverse events, to a business imperatively responsible for risk assessment, risk management and risk mitigation. The volume and complexity of drug safety data that is captured, processed, analysed and reported has grown substantially. Regulatory oversight of company safety activities for approved pharmaceutical products is now much more holistic than the previous limited view of assuring adequate and compliant procedures that licence-holders established to meet their legal obligations. Regulations are targeted towards strengthening companies’ PV systems and defining clear roles and responsibilities across both the regulatory agencies and the industry. The present largely reactive system is being transformed into one that is proactive, robust and more useful clinically.

All of the above developments have resulted in an acute need for companies to optimise their PV systems and processes. They have led many companies to outsource safety operations to specialised providers who have the required scientific expertise as well as operational excellence to provide effective and cost-optimised solutions in a globally distributed model. Operational complexity increases with the inclusion of multiple groups and hand-offs. The core challenge, in this rapidly evolving environment, 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.

With increased emphasis on quality and compliance, regulatory agencies have made it clear that quality is integral to product safety and PV quality systems constitute the foundation of PV operations. The International Conference on Harmonisation (ICH), European Medicines Agency (EMA) and US Food and Drug Administration (US FDA) have laid out their expectations with respect to quality management systems (QMS) for PV. The regulatory expectations mentioned and analysed in this article are based on EMA’s Good Pharmacovigilance Practices (GVP) Module I – PV Systems and their Quality Systems1 and on FDA’s Guidance for Industry – Good PV Practices and Pharmacoepidemiologic Assessment (Mar 2005)2. Though a lot of ICH3 and FDA4 quality publications relate to manufacturing, there is an expectation that these will also be applied to PV. FDA’s Office of Regulatory Operations has also issued the ORA Quality Manual in March 20125.

What is a QMS?
EMA’s GVP Module I enumerates the following quality objectives of a PV system:

- Complying with legal requirements for PV tasks and responsibilities
- Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure
- Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public
- Contributing to the protection of patients’ and public health

The goals of a QMS are compliance with the law, prevention from harm, promotion of safe drug use and patient/public health protection. Quality documents and guidances across regulatory bodies state that a QMS addresses quality planning, quality adherence, quality control/quality assurance and quality improvements, and comprises of organisational structure, responsibilities, procedures, processes, resource management, compliance management and record management.

Organisational structure, responsibilities and resource management pertain to the availability of a sufficient number of competent and appropriately qualified and trained personnel with clear roles and responsibilities (job descriptions), and also pertains to the availability of other infrastructure such as computers and facilities. Quality planning is about being prepared for and anticipating issues and problems, along with the need to stay up-to-date on new regulations, technology and processes.

Compliance management refers to the need to have execution and controls...
in place to manage compliance with requirements outlined by the Competent Authorities (CAs) with respect to quality, completeness of PV data, assessment and timeline compliance, independence of PV activities and effective communication. A key element of compliance management is to have valid, traceable processes with audit trails and to have the right technology. Other aspects of compliance management are defining and monitoring of key performance indicators (KPIs), ensuring root cause analysis (RCA) and corrective and preventive action plans (CAPAs) and conducting periodic audits. Compliance management processes to monitor the performance of a PV system also include evaluation of the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients. Given the complexities of safety evaluation and reporting, compliance management thus subsumes a majority of the elements of operational excellence which are critical to ensuring quality and compliance of a PV system.

Record management is about documentation of a quality system; everything should be documented in a systematic and orderly manner in the form of written policies and procedures, quality manuals and quality records. Data security and privacy are critical requirements. Quality system documentation by the marketing authorisation holder (MAH) in the PV system master file (PSMF) is also a part of record management.

Most of the above requirements are similar in the FDA and EMA guidances. The EMA has more requirements, for example, with respect to training (even personnel with no direct PV responsibilities are required to have adequate training) and is more specific and explicit in stating certain requirements, for example, the compliance management elements which are mentioned above.

EMA identifies certain PV processes as critical, and quality requirements for these processes are outlined in the respective GVP modules. PV processes identified as critical include:

- Collection, processing and reporting of individual case safety reports (ICSRs) from any source
- Signal management
- Aggregate safety reporting/periodic safety update reports
- Meeting commitments and responding to requests from the CAs
- Interaction between PV and product quality defect systems
- Communication about safety concerns and changes to the benefit-risk profile between MAHs and CAs, and also notifying these changes to the patients and healthcare professionals
- Keeping product information up-to-date
- Implementation of variations to marketing authorisations for safety reasons

Aspects of Operational Excellence and Oversight in QMS

Until about 2009, compliance to reporting timelines of expedited reports by the MAH was the only valid metric of the effectiveness of an AE processing operation evaluated by global health authorities. Driven by the public focus on drug safety led by recalls of a few prominent drugs, the regulators began to look closely at the way the pharmaceutical companies were classifying cases. Suspected unexpected serious adverse reactions (SUSARs) are reportable under existing guidelines, whereas AEs listed on a drug label are normally not reported individually but are compiled into aggregate periodic reports. There were some findings from US FDA inspections of questionable criteria being used to ‘downgrade’ reportable SUSARs. As a consequence regulators started looking closely at ‘case quality’.

Collection, processing and reporting of ICSRs is often outsourced since it is resource-intensive, primarily process-driven and largely operational in nature. MAH oversight of outsourced processes is increasingly coming under regulatory scrutiny.

Increased complexity of drug safety monitoring, increased volumes and greater regulatory and public scrutiny, along with the ensuing need to outsource parts of the process have enhanced the focus on operational excellence. It is critical to outline the systems, processes and other tools and controls which the MAH will use to achieve operational excellence, thereby ensuring quality and compliance. Irrespective of whether PV is done in-house or is outsourced, description of such systems, process and tools is an integral part of the QMS. When parts of the process are outsourced, measures taken to achieve operational excellence are often outlined as part of the oversight plan of the MAH. Thus specification of how the oversight will be provided, the tools and controls that will be used, has become an important component of the QMS.

Relevant details of the processes, measures and controls are included in a quality agreement and/or a quality management plan (QMP) and an oversight and/or governance document signed by the MAH and its PV partner. These include the KPIs which will be used to monitor performance, how they will be measured, what are the thresholds, for example. The oversight/governance document mentions how operational and management teams from both organisations will monitor the performance of the PV system, the escalation and resolution mechanism, the communication channels and individual roles, responsibilities and accountabilities. There may be an oversight SOP in some cases.

Some of the KPIs used to monitor performance of the outsourced operations and which constitute service level agreements (SLAs) are:

1. regulatory reporting compliance (per cent cases submitted to regulators on time);
2. case quality metrics;
3. case turnaround time (internal case processing timelines);
4. number of daily case closures.

Depending on the size of the outsourced operations and the processes which are outsourced, other factors such as deviation from planned volume per week or per month, system uptime, in-bound late cases and employee turnover may also be monitored as KPIs. The KPIs constitute operational excellence parameters and measuring and tracking them is a way to achieve operational excellence.

The QMS, through the quality agreement or QMP, outlines the process
for documentation and evidence of monitoring of KPIs and may also include aspects of governance and escalation mechanisms. It should also contain some description of how the MAH will oversee other aspects of the outsourced operations on a day-to-day basis, for example, ensuring that adequately qualified and experienced individuals are recruited, required training is conducted and documented, individuals are signed-off on the project based on pre-defined criteria, ensuring adequacy of infrastructure and facilities of the service provider. The QMP may also include details of any process improvements/enhancements which may be applied for attaining operational excellence and ensuring compliance. These details may include six-sigma or lean methodology applied to improve the process, automation of parts of the process to minimise the risk of errors and misses, additional quality gates and any templates, tools, checklists, that may be deployed. The QMP thus drives operational excellence and also enables effectiveness measurements.

**Case Quality**

The ultimate objective of all these processes and control mechanisms described above is to ensure quality and compliance of the PV system. Reporting compliance is of utmost criticality and operational excellence methods are instrumental in helping achieve this, especially when volumes of cases/reports are large. But quality is also increasingly being scrutinised and it is intertwined with compliance. For instance, in the case of ICSR processing, wrong event coding, wrong assessment of seriousness or listlessness and wrong identification of Day 0, could lead to non-compliance on reporting timelines. Thus, ensuring good case quality becomes a prerequisite for ensuring compliance. Besides, if the quality of the case narrative is poor, even for non-reportable cases, its impact on the quality of evaluation and reporting of aggregate safety may be substantial. Hence, in a way, good case quality is the foundation of a good quality PV system.

Beginning 2009 when the UK MHRA and EMA (Volume 9A) provided guidance on what they considered “acceptable” case quality, much of the industry used ad-hoc measures to assess the quality and overall disposition of the cases. In February 2011 the MHRA published ‘Best Practice in Reporting of ICSRs’ that outlines quality expectations in the context of E2B submissions. In view of the subjective nature of case assessment and further variability that is introduced in the process when it is outsourced to third parties, regulatory authorities like the MHRA have defined specific expectations of case quality and of third party case processing. The US FDA has not yet defined what they expect from “good” quality cases. Over the past few years, companies started to baseline their operations and establish measurement criteria to comply with the newly articulated expectations of the health authorities. There is wide variation in what each company expects as operational metrics to measure quality of cases they report to the health authorities. This is due to the inherent variability in medical assessment of causal relationship between a reported AE and a suspect drug, as well as assessment of seriousness of the AE given the confounding factors such as concomitant medications and concomitant medical conditions. Thus, there aren’t any industry-wide benchmarks for quality.

The quality of a case may be measured in terms of case level quality or field level quality. The data fields may be weighted in order to come up with a weighted measure of quality. Some companies may prefer to categorise errors into critical and non-critical, some may categorise them into critical, major and minor, while some others may want to consider all errors on par, regardless of their criticality. The number of data fields reviewed to find errors can also vary widely; for example, it could be as low as 4 or 5 and could be as high as 50 to 60. The SLAs also vary accordingly.

**Conclusion**

The QMS is essential to, and needs to drive, the biopharmaceutical PV operations. It is not a mere obligation or a mandate. It needs to be a living system that determines the way the PV system works in the company and needs to lay down the framework that guides compliance and quality of the PV system. Whether explicitly stated or not, all guidelines have similar expectations from a QMS, though some are more specific than others. In the context of increased outsourcing of PV operations, particular relevance are the components of the QMS that outline how operational excellence will be achieved, how it will lead to better compliance and quality, and how effective oversight will be provided. The prescribed framework of the QMS which includes quality planning and compliance management requires focus on methods and tools to drive operational excellence, resulting in enhanced quality and compliance. These components of the QMS are also increasingly coming under regulatory scrutiny.

References

1. Guideline on good pharmacovigilance practices (GVP), Module I – Pharmacovigilance systems and their quality systems; EMA, June 2012
3. ICH Quality documents Q8, Q9, Q10, Q11
5. ORA Quality Manual, March 2012, Document # ORA-QMS-POL.002, version #2.0, Department of Health and Human Services, FDA Office of Regulatory Affairs and Quality Management System