Pharmacovigilance: Why Are So Many Companies Failing their Regulated Audits?

When EU legislation on pharmacovigilance came into force in July 2012, it established the clear legal requirement that marketing authorisation holders must perform audits of their pharmacovigilance systems, including risk-based audits of their quality systems.

So why then are so many life sciences companies struggling with associated audits and inspections? Summarising the 10 aspects of PV covered by the formal requirements, Vanessa Fachada Oliveira, Pharma-covigilance Manager & EU QPPV at Arriello, discusses where companies are falling short and where they need to focus their attention to stay on the right side of inspectors.

The way life sciences companies run, check and document their pharmacovigilance (PV) activities is as important as the function itself, because regulating authorities need to be confident that standards are being upheld and that nothing is being missed. So it is vital that pharmaceutical organisations get this right and can provide evidence of strong standard operating procedures on demand.

Yet, although eight years have elapsed since EU legislation on PV came into force, a majority of companies are still struggling to fulfil their obligations, potentially causing marketing authorisation holders (MAHs) to fail inspections, incur fines and see products withdrawn from markets.

One of the reasons for common failings in PV process documentation is that the EU has not set out clear guidelines about how or where companies should go about this. Here are some of the problems this can cause and what can be done to rectify the situation:

1. **Failure to implement an adequate quality management system.** EU PV legislation makes clear that quality systems should form an integral part of an organisation's PV system. But although other strong standard operating procedures (SOPs) may have been documented as part of general quality systems, there is often nothing relating specifically to PV – about procedures for managing deviations; what happens if a new qualified person responsible for pharmacovigilance (QPPV) is appointed; how external service partners are qualified; what the business continuity plan is and how this is tested, etc. These omissions can result in inadequate integrity and management of pharmacovigilance data; difficulty identifying and implementing corrective/preventative actions (CAPAs); and incomplete oversight/compliance management of a PV service provider.

2. **Insufficient or poorly documented training.** This can occur firstly because it is not obvious who is responsible for or who actually *needs* PV training. Depending on the organisation, the remit for organising training could fall to the HR department, the quality leadership, or the PV function itself. What's less obvious is that *everyone* in the company will need PV training – from the most senior managers to manufacturing teams. That's because anyone could find themselves the recipient of safety feedback, which means everyone needs to know what action to take next – and how quickly. To ensure that no training needs are missed, there should be a clear training plan, and formal records showing which employees have attended which sessions and when. The QPPV in particular must attend regular training and have up-to-date certificates. Quality people who perform audits must have at least some PV training too, yet this is often found not to be the case.

3. **Failure to make contractual provision for PV along the supply chain.** Manufacturers as well as MAHs and distributors could find themselves the first port of call for a safety report. A safety data exchange agreement should set out the respective PV responsibilities of each party, who the QPPV is, who will manage actions relating to adverse reactions and associated reporting. For a distributor, the obligation might simply be to forward all relevant information to the MAH – unless that company also has a remit for local PV activities. Lesser failings, but nonetheless important to put right, include the omission of situation reports, and provision for archiving, retention periods and exchange of information following the termination of an agreement.

4. **Inadequacies relating to the pharmacovigilance system master file (PSMF).** This is one of the main documents of the company's PV system, which should provide a very clear overview of all critical PV processes and procedures for managing adverse events and safety signals; the key stakeholders; full details of the QPPV and their experience and contact details; documentation showing how the organisation will manage compliance with the legal requirements; KPIs and the rationale behind these. The PSMF must be kept up-to-date at all times, so there must be a process for ad-hoc revisions as well as periodic updates. If the competent authority asks to see a copy of the file, the company must be able to deliver a fully updated document within seven days. Failings can be for something as simple as poor formatting or omitting an index to allow easy navigation. If the PSMF preparation is subcontracted, another oversight inviting a penalty might be the lack of MAH involvement in any document revisions.

5. **Inadequate QPPV oversight**. If the qualified PV person – who carries personal liability for PV failings, in addition to any company penalties – does not have sufficient oversight of the process for safety variations preparation, submission and implementation, or over KPIs and ICSR adverse event reporting, this could also result in a failed inspection and potential fine.

6. **Lapsed attention to risk management.** This is one of the topics with the largest number of critical findings over time during inspections, and includes findings related to poor maintenance of product information (routine risk management) or to implement additional risk minimisation measures (aRMM), such as educational materials or pregnancy prevention programmes.

7. **Inconsistent or inadequate collection and management of safety information.** Often the breakdown here is a failure to identify and track all potential sources of spontaneous safety data, or to reconcile adverse event monitoring activity with medical information and product quality complaints. This can lead to safety signals being missed. Failing to properly validate the database for ICSR management can also lead to a fine, especially for SMEs which can't justify the cost of a top-of-the-range PV database. Using spreadsheets or other tables to manage validation is not acceptable, but there are affordable options to formalise activity here. Failure to transfer safety data from previous MAHs during an acquisition can also catch companies out.

8. **Ongoing safety evaluation failings.** These concern benefit-risk and signal management and aggregate reports (PSURs). Common mistakes include inaccurate sales and patient exposure figures; the inclusion of unrelated adverse event reports; failure to include relevant cases in the benefit-risk analyses; and late updating of product information. Other issues include failure to discuss all sources of potential signals; and a lack of rationale for the report frequency.

9. **Poor integration/interfaces between departments or with external parties to support complete and timely safety information.** It's important to include teams monitoring MAH websites for comments/safety reporting, and keep tabs on any general company email addresses that people might use to report safety data.

10. **Failure to ensure safe archiving/backups and business continuity planning.** This includes validating controls over access to sensitive patient medical information and, if fireproof/waterproof filing cabinets have been swapped for digital archiving, that such systems meet all required parameters.

With so many elements to get right, it is unsurprising that PV departments are getting some of this wrong – and feeling daunted by the responsibility.

It is worth seeking unbiased feedback on current provisions from professionals with experience of a diverse range of approaches and systems, who can bring to bear the latest best practice – or perform a gap analysis that can help target remedial action.

In due course, the EU should clarify and update its guidance, so pharma companies understand more of what to aim for. But it's important not to wait until then: competent authorities are starting to perform remote inspections, which is likely to lead to increased coverage and frequency as auditors' capacity is increased.

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