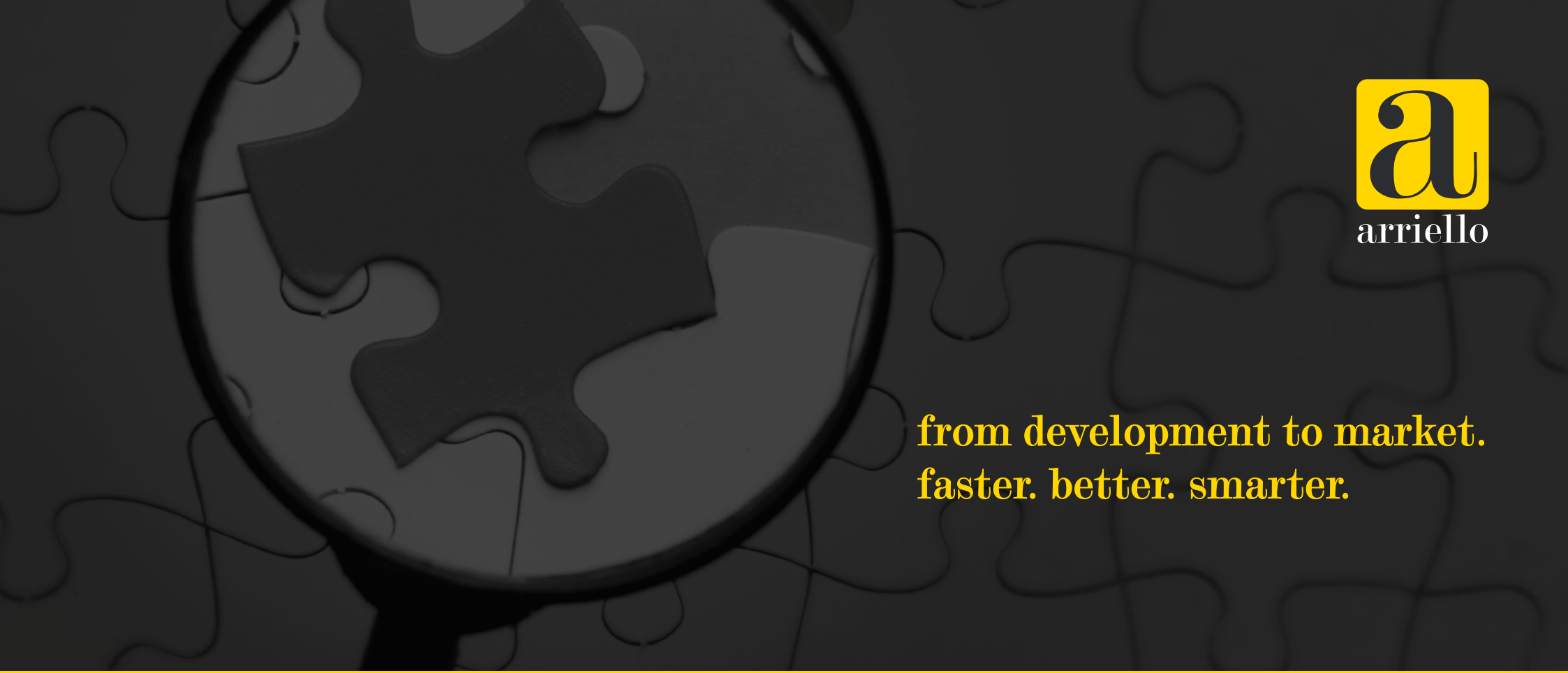

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PV Audit Success Guide.

Pharmacovigilance audit failures. What's still going wrong?

The author.

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Foreword.

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?

This guide summarizes the 10 aspects of PV covered by the formal requirements, where companies are falling short and where they need to focus their attention to stay on the right side of inspectors.

"Audits and auditing have been one of the greatest sources of professional development during my career. I see audits as an opportunity to learn, share and improve pharmacovigilance systems; improving what we do and how we do it.

It's also an opportunity to gain a better understanding of our systems against pharmacovigilance guidelines and best practices. Audits should therefore be viewed for the positive changes they can bring, but first, let's make sure we don't fail them, and hopefully this guide will help."

Vanessa Fachada Oliveira
Pharmacovigilance Manager & EU QPPV at Arriello

Why so many companies fail their regulated audits?

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potentially causing marketing authorisation holders (MAHs) to fail inspections, incur fines and see products withdrawn from markets.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.

Typical 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.

... more examples of typical problems and solutions.

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 PV 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 special 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; Key Performance Indicators (KPIs) and the rationale behind these.

The first version of the PSMF needs to be in place **prior to MAA submission**. Although it is acceptable that some information is not provided in the initial document (such as compliance detail), descriptions of **what will be implemented** should be provided.

The PSMF must be kept up-to-date at all times, so there must be a process for ad-hoc revisions as well as periodical 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.

QPPVs need access to the PSMF and authority over its content, especially when the PSMF is in a different location. Additionally, it is also important to guarantee that the QPPV has access to the global safety database.

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 Individual Case Safety Report (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 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.

... more examples of typical problems and solutions.

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 Small and medium-sized enterprises (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 web sites 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.

Summary.

Bring in the best practice.

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.

10 typical reasons why companies fail their audits.

1. Inadequate quality management system.
2. Insufficient or poorly documented training.
3. No contractual provision for PV in the supply chain.
4. Inadequacies relating to PSMF.
5. Inadequate QPPV oversight.
6. Lapsed attention to risk management.
7. Inadequate management of safety information.
8. Ongoing safety evaluation failings.
9. Poor interfaces between departments / external parties.
10. Safe archiving/backups and business continuity planning.

Case study.

Pharmacovigilance inspection: Creating a winning approach.

US Global Biotechnology Firm

Established: 1992

Company size: 2,400

Acting as the local person responsible for pharmacovigilance (LPPV) for a US biotechnology firm, our local vendor had a complex task on its hands. The Croatian national health authority (HALMED) had contacted and tasked them with performing an on-site audit for all our client's pharmacovigilance activities in Croatia to see whether our client met all local regulations and requirements.

Requiring support, the vendor turned to Arriello, and we were soon preparing both the vendor and its client for the audit.

Challenges.

Preparing for the inspection meant navigating the various roles and responsibilities of Arriello, the vendor, and our client. Numerous individuals from different locations and time zones were involved, raising the risk of miscommunication and information being delayed due to time differences.

Coordination was critical. When authorities requested information, we had to pull data from all parties and synthesize it.

When auditors asked for information, we needed to act as a mitigator between our client and our local vendor to prepare and provide documentation. Overcoming time and location differences, we had to enable all parties to function efficiently to support the flow of documentation.

Solution.

To ready our client for the inspection, we executed a set of oversight activities, such as holding weekly preparation meetings, defining roles and responsibilities, and more.

We thought outside the box and predicted potential questions. Months in advance, we also began collecting the required documentation, placing records in the cloud for quick retrieval during the inspection.

With the agenda from HALMED, we assigned the roles and responsibilities for individuals needing interviews. We gathered intelligence on similar inspections from other clients such as the inspecting style of the health authority and shared this data with our local vendor and our client.

Faster. Better. Smarter.

With Arriello's faster, better, smarter approach, the vendor successfully passed the audit. Our team fostered collaboration, strong project management, a quality system, and adherence to processes, delivering faster results that avoided delays in the inspection timeline. While the project was complex, our communication and partnership with all parties empowered us to achieve a common goal together.

This winning approach went beyond a successful inspection... creating an experience our client called "phenomenal."

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About us.

Arriello has been a leading provider of risk management and compliance services to the Life Sciences sector since 2008.

These include Market Consultancy, Global Regulatory Affairs strategy and implementation, Full and Local Pharmacovigilance solutions, Clinical Drug Safety, and Quality and Compliance auditing and systems.

Our brief is simple; to make the process from development to market faster, better and smarter.

Headquartered in Ireland, with European operations in Central Europe, we provide expert Market Access guidance across the EU, US, LATAM, CIS, MENA, Asia and South Africa.

With our extensive global vendor network, ISO 9001 certification, years of experience and satisfied clients, including Global Originators, Biotechs, Generics and CROs, you can be confident in our ability to deliver.

However complex or simple your requirements, you can rely on us as a trusted partner.

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