

Inspections: How To Turn Yours Into A Positive Experience

By Dr. Iain Cockburn, MBChB, MRCCP, MFPM, FFPM
in conjunction with Harten Group



Dr. Iain Cockburn

With Inspections becoming increasingly frequent and more rigorous across Europe, how can you ensure that if you have one it is informative, constructive and helpful rather than negative for the company's credibility and image?

The legal framework

Firstly it is important to understand the legal framework. The Market Authorisation Holder (MAH) must ensure that they have an appropriate system of pharmacovigilance in place to assure responsibility for their products on the market and ensure that appropriate action can be taken when necessary.

This includes one QPP responsible for pharmacovigilance at all times within the European Economic Area and the establishment of a system to collect, prepare and submit expedited adverse drug reactions and periodic safety update reports to the competent authorities.

What should this 'system' include? It needs to have a mechanism for expedited reporting, producing periodic safety update reports, responding to requests and handling urgent safety restrictions. Also essential are ways to carry out continuous monitoring of the safety profile, notify authorities of changes to the B/R profile, meet CPMP post-authorisation commitments and conduct internal audits.

Inspection procedures

In order to conform, the inspectors will expect procedures covering the maintenance of address and contact details, particularly for the QPPV and the deputy QPPV. An up-to-date list of EU and UK products is also essential, as well as a list of clinical trial medicinal products.

Also essential are fully prepared and maintained formal description of the Pharmacovigilance Systems, together

with a global and local index of standard operating procedures. A database description and database documentation including validation, security, data lock, back-up, disaster recovery, use and quality control will also be required, together with details of relevant PV contracts and safety agreements.

Risk management plans should be on the list as well as documents outlining the roles and responsibilities of the EU QPPV and PV physicians.

When it comes to systems concerning quality these need to cover PV, training procedures and records, management of standard operating procedures including approval, security and maintenance and QC procedures, together with QA auditing of PV systems.

Data handling and how you manage both spontaneous adverse drug reactions and clinical trial suspected unexpected serious adverse reactions are also a requirement, together with responses to PV queries by regulatory authority and healthcare professionals and literature searches.

There should also be a procedure for signal generation and trend analyses, continuous review of ADR reports, PSUR production and review and Management of Urgent Safety Restrictions. Handling of Summary of Product Characteristics (SmPC) variations and archiving and retrieval of PV documents are also important. Inspectors will also look for procedures relating to the interface with other departments – including medical information, product quality, marketing and regulatory affairs.

What are the triggers for inspections?

Some common reasons for an inspection being instigated include: a new centrally approved product – usually within six months of it going on the market, manufacturer safety communication without prior approval from concerned authority, significant non-compliance in

... if you understand your requirements, have good systems, document your activities and conduct good pharmacovigilance practice, you should have nothing to fear with your next inspection.

adhering to reporting time-frames for expeditable or periodic safety update reports or when a previous inspection has brought up 'critical' findings.

In the UK, if you have a product marketed in the UK you should expect a routine inspection every two to five years. Normally you would receive forewarning of a planned routine inspection several months in advance. This would be followed by a request for a description of your PV systems and once received would be followed by a proposed agenda which can be negotiated in terms of timing but not of content.

What happens during an inspection?

During an inspection, target areas may include a review of internal documents, 15-day reporting compliance statistics, and a sample of periodic safety update reports. Other typical areas are literature searches and trend analyses, a systems overview, looking at standard operating procedures, organisational charts, database details and adherence to any Risk Management Plans.

It's important to remember that inspectors can go 'off scope' at any stage if prompted by on-site discoveries. For example, there has been one instance where a sales representative was asked to prove that he had the current SmPC for his products in his car. He didn't and this led to an immediate 'major' finding. Another example was where the inspector noted an unreported expeditable report arising from a clinical trial, marched round to the Clinical Research department to interview the responsible Medical Monitor and this triggered a full scale GCP Inspection – two hits for the price of one!

Typically, however, they will drill down on a few key areas such as expedited reporting – what was the recorded date of receipt? Was there a complete failure to report? Or was it late? What is the quality of the reports (such as comparing MAH and HCP dual reporting)? Are there any missing reports? Can they see examples of post-authorisation study reports and periodic safety reports? What is the quality against the source? Was the follow up adequate?

In terms of periodic safety update reports – was there a complete failure to report? Was it done at an inappropriate time? Was any information concealed? Were there any changes to RSI or actions taken for

safety reasons? Was the quality poor in terms of individual case histories? Perhaps the assessment was poor with missed new signals? Or the latest Company Core Data Sheet (CCDS), perhaps there were differences with the SmPCs not addressed in the covering letter? Or maybe previous requests from competent authorities have not been addressed?

Another popular area for focus is responding to authority requests for further information. Have these been untimely? Was there a failure to respond to post-authorisation commitments? Or was the quality of response poor?

Are there any typical non-compliance findings?

Although each individual inspection can cite different findings, there are some more common non-compliance findings described by the MHRA.

Some of these centre around the QPPV who may lack complete and prompt access to safety information, not be sufficiently involved in periodic safety reviews, risk management plans and/or urgent safety reviews, has inadequate delegation procedures in place or inadequate access to medical safety experts. If the company has its PV headquarters in a third country, maybe the QPPV has very limited access to the PV database or is the QPPV lacking in training or experience?

In the area of suspected serious ADR reports, there could be significant non-compliance regarding timely reporting. One authority, the MHRA, has declined to publish acceptable compliance rates for expedited reporting but figures between 95-98% have been quoted by some manufacturers. Maybe there is an inadequate procedure for identifying duplicate reports or a lack of appropriate and timely follow up of ADR reports.

Other issues may involve a poor contract with partners, inadequate disaster recover, violation of UK legislation such as failure to unblind clinical trial expeditable reports prior to submission, poor quality control at various stages of ADR reporting, inadequate pharmacovigilance training for sales representatives, a failure to adhere to EU data protection law when transferring data outside the UK – this is particularly relevant for safety databases in multinational organisations – or a lack of QA of pharmacovigilance activities.

What do the results mean?

Findings are divided into 'Critical' (those that are likely to significantly damage public health or major regulatory non-compliance), 'Major' (may lead to significant damage of public health or non-compliance) and 'Other' (remedial actions required to avoid future damage to public health or potential non-compliance).

A 'critical' finding not only requires urgent remedial action, but is automatically communicated to other European authorities, as well as the FDA. Significant non-compliance, in particular failure to carry out any CAPA (corrective and preventive actions), will lead to escalating punitive measures which may include product suspension and license revocation, 'name and shame', and fines and/or imprisonment of the principals (e.g the QPPV, Managing Director). In some countries, fines have included 10% of annual turnover – a substantial penalty! A good example of significant non-compliance would be an instance where a critical finding is not ameliorated in a timely manner.

In practice, however, inspections are usually conducted professionally and are informative, constructive and helpful. They rarely point out individuals in case of any findings but rather focus on system defects. They can also be a useful justification for increasing resource or enhancing existing systems.

In summary, if you understand your requirements, have good systems, document your activities and conduct good pharmacovigilance practice, you should have nothing to fear with your next inspection. Instead, you will see them as an opportunity to reflect on the standard of your systems and bring much-needed recognition of your work!

Harten Group is a leading provider of PV consultancy services, from selecting an interim to deliver immediate operational assistance to meet a short-term need to carrying out a strategic review of a wider drug safety issue. With over 350 specialist PV consultants registered on its network, it has supported 100 companies' drug safety operations, on a wide range of PV projects over the last 16 years.

Tel: 01223 233777

www.hartengroup.co.uk