

# Systems Audits in Pharmacovigilance

Michaela Rittberger, Michael Stegemann, and Jürgen-Hans Schmidt

*In the light of the changing legal situation for pharmacovigilance, the conduct of an audit in this area has an increased impact on assuring and/or improving the quality of the processing of pharmacovigilance data as part of the respective pharmacovigilance system.*

*This is especially true as the pharmacovigilance process becomes increasingly globalised and complex, while the necessity to meet timelines and the need for effectiveness remains as important as ever.*

*This chapter describes the performance of a pharmacovigilance audit, from the audit planning to writing an audit report. It gives an overview of several aspects of audit conduct. Moreover, experiences with inspections and common audit and inspection findings are described. However, this chapter should not be understood as a comprehensive working instruction and not be regarded to reflect all possibilities and aspects of a pharmacovigilance audit.*

## 1. Introduction

The purpose of pharmacovigilance (PhV) is to provide accurate, complete and timely information about the benefit-risk profile of medicinal products throughout their life cycle to interested parties (e.g. company management, trial subjects, consumers, healthcare professionals, authorities).

Therefore, pharmaceutical companies need to maintain a system that ensures

- An active, systematic and continuous monitoring of pharmacovigilance cases received.
- Early detection of any regular safety signals or irregular crisis situations.
- That appropriate actions are taken to minimise risks and prevent harm to the company and customers.

The quick and effective identification and evaluation of pharmacovigilance signals is dependent on early access to complete information. This is essential for the Marketing Authorisation Holders (MAHs) as well as Marketing Authorisation Applicants (MAAs) and competent authorities to be able to protect public health in taking appropriate actions swiftly.

Signal detection should identify this problem at an early stage.

Principles of signal detection in pharmacovigilance: "... Although pharmacovigilance is especially concerned with adverse effects a signal is more broadly defined as a set of data constituting a hypothesis that is relevant to the rational and safe use of a drug in humans ..." [1].

Procedures for the detection of safety signals, based on pharmacovigilance data, should be complemented by a risk management system.

A risk management system should be understood "as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions." [2]

At the time of this publication much relevant legislation and many guidance documents had been changed as well as developed, and a lot of work is still in progress to this end. As a consequence of the rapidly changing legal situation, several points need further clarification and not all questions have been answered until now.

However, one result of the changes in legislation and guidance is that more EU member states are implementing routine pharmacovigilance inspection programmes.

There is, therefore, an increased focus on pharmacovigilance activities, which result in an increased number of PhV inspections. These focus on whether pharmaceutical companies maintain a reliable pharmacovigilance system fit for the purpose mentioned above.

To meet the increasing legal and business requirements, systems audits in pharmacovigilance can evaluate whether the system is designed to ensure that activities applied therein are performed in compliance with applicable requirements. Failures, areas of improvement and the need to initiate corrective and preventive actions can be identified.

In addition, systems audits can encourage a continuous improvement process as understood by ISO 9004:2000 [3].

This publication focuses on the performance of systems audits in pharmacovigilance for medicinal products in human use concerning the pre- and post-authorisation phases. In this context experience already gained in common inspections and audit findings will be presented.

## **2. Audit methodology**

### **2.1. Objectives of a pharmacovigilance systems audit**

The following five audit objectives are proposed as being systematically applicable to pharmacovigilance units to independently confirm that:

- the organisational unit responsible for pharmacovigilance is capable of performing all related tasks.
- interfaces, e.g. to product quality, regulatory affairs, marketing, are regulated and functioning.

- the processes established are performed in accordance with external and internal quality requirements.
- the safety data received and processed in the database(s) are consistent with the source documents and are evaluated and timely reported to all relevant parties.
- there is a quality management system in place supporting continual improvement of the pharmacovigilance system.

## 2.2. Audit planning

In order to be customer-oriented and to set up an optimal operational course for the audit, the planning should be done in close cooperation with the auditees and the responsible line management (called process owner in the following).

If the individual audit of a pharmacovigilance unit is part of a systems audit programme, the audit planning would be based on the latter. In this programme, the focus of the individual audit would already be determined. For the audit planning the following basic elements need to be clarified or done first:

- The audit setting (organisational unit, auditee, process owner, locations, duration of the audit, staff to be contacted, auditor with contact details).
- Listing objectives, scope and topics of the audit.
- Defining applicable external and internal quality standards.
- Selecting elements of the quality management system (e.g. quality manual, job descriptions, resource management, training activities, Standard Operating Procedures (SOPs) management, facilities).
- Selecting processes (specifying how the functionality will be evaluated: either by checking the quality of the process outputs, e.g. the individual cases or safety reports, or rather by reviewing the process flows for adherence to the SOPs and for efficiency).
- Existing quantitative quality parameters for corresponding processes (e.g. a maximum acceptable number for late cases is defined); determining them, if applicable.
- For the review of case processing, defining an observation period and the sampling approach.
- If applicable, check if special safety monitoring programmes are implemented.
- Involvement of pharmacovigilance interfaces (e.g., regulatory affairs, pharmaceutical production, marketing, or clinical development; their agreement on audit support is to be obtained first).
- Outlining the audit report flow, option of a draft report, and timelines for reporting.

When selecting an auditor or audit team, adequate qualification of the audit staff should be confirmed. Auditors should be familiar with international and applicable local regulatory requirements on pharmacovigilance,

have been trained on such audits preferably in co-audits, be experienced and familiar with the systems audit approach (e.g. in terms of DIN ISO 9001 norms on quality management system).

### 2.3. Audit preparation

Logistical and content aspects of the audit would be worked out in more detail in this phase.

The duration of the audit depends on the scope of the audit, number of audit staff, location(s) to be visited, availability of staff, types and number of safety cases to be reviewed. An audit agenda can structure all this information.

It is crucial to obtain all necessary information about the pharmacovigilance unit to prepare the audit effectively. The following documents (copies) should be requested:

- Summary of pharmacovigilance system (SPS).
- Organisational charts.
- Further important quality documents, e.g. specific policies, SOP index, selected SOPs, quality monitoring plans, e.g. with Contract Research Organisations (CROs).
- List of investigational/ marketed products included in the safety surveillance.
- Survey on co-development and/or co-marketing (license partners) affecting safety reporting procedures.
- Description database(s) used (requesting read access) during the audit.
- Status of safety cases processed in the defined audit observation period.

Familiarisation with process descriptions is mandatory to understand how the processes are organised in detail and how to derive audit questions.

Due to the usually high number of cases processed, the sample size for cases to be audited needs to be calculated. If quantitative acceptance values were, for example, specified for the case processing time lines, these limits – so-called Acceptance Quality Limits – would be used as an audit reference.

If possible, an electronic export of relevant data might be requested from the pharmacovigilance database. Such requests can be made quite early to allow for a pre-check of data and of any technical adjustments, if necessary (compatible data format).

The preparation phase would be completed by an official announcement letter to the auditees, providing all information on audit timing, location, required availability of staff, documents, database access, work space, etc. The audit agenda would be attached to this letter.

### 2.4. Audit conduct

The conduct of pharmacovigilance audits is very similar to that of other systems or process audits. A generic sequence of audit topics is proposed that is to be adapted according to the actual scope of the audit:

# Audits in Data Management, Statistics and Medical Writing: Auditing Clinical Databases, Trial Reports and Related Systems

Rita Hattemer-Apostel and Wolfgang Reinhardt

*Audits of clinical databases and statistical or integrated clinical reports are usually complex and time-consuming activities. They involve reviewing a multitude of different documents and the audit processes are interdisciplinary involving personnel of data management, statistics and medical writing departments. Audits in this stage in a clinical trial are complex and errors are likely to occur. The scope and procedures for conducting audits in the field of data management, statistics and medical writing are described in detail. Database audits and trial report audits may be the 'nucleus', the core component of systems audits in data management and medical writing, respectively. The chapter describes how database and report audits, initially focused on an individual clinical trial, can be expanded into systems audits, exploring underlying processes and procedures in data management, statistics and medical writing departments. Several other aspects of auditing are discussed, including specification of the audit sample size, the evaluation of error rates and audit observations as well as the subsequent follow-up activities. Finally, a list of frequent and typical audit findings observed in database and report audits is included.*

## 1. Introduction

Quality assurance (QA) audits conducted in the final stages of a clinical trial, i.e. audits of the clinical database, the statistical analysis and the integrated report can contribute to increased reliability of study results described in the final report. The final report is the document submitted to the regulatory authorities in an application for drug approval. Therefore, the report can be considered the essence of a trial and the report describes – in a condensed way – the various processes from the initiation of study sites, the conduct of the trial at the investigator sites and data management,

including the statistical analysis and biometrical/medical interpretation of the trial results. Audits, at this stage of a clinical study, are worthwhile since their objective is to carefully assess the validity of the data processing and analysis and ensure that the clinical report provides an accurate portrayal of the trial data and that valid conclusions are drawn from the data.

As audits are performed to uncover existing and potential deficiencies in an early stage of a trial and, thus, should lead to an overall quality improvement of a project, it seems to make little sense to conduct audits at a relatively late stage of a clinical trial after all data has been gathered from the sites. However, at no other point in a clinical trial, data are so often corrected, converted, transformed, saved, and analysed than in this stage. As a consequence, audits in this phase of a clinical trial prove to be important with regard to the validity of the data in the clinical report and the preceding data 'cleaning' procedures. Integrated trial reports of high quality are only achievable, if an overall quality management system assures that the Case Report Form (CRF) data are accurately reflected in the database, in the subject listings, tables and figures and that these data are free from any implausibility.

The chapter aims to describe fundamental aspects of audit planning and conduct for the areas of data management and the drawing up of trial reports. In addition, procedures such as the definition of the audit sample size (sampling), the specification of acceptable error rates and the follow-up and assessment of audit findings will be discussed.

## **2. Audit scope and procedures**

### **2.1. Data management**

Data management is the process in which data recorded in the CRFs, laboratory results, as well as other examinations are transformed into data which are statistically analysed and clinically evaluated in the trial report. The regulatory authorities will decide whether the drug or device may be approved on the basis of the trial report. On closer examination, the process of data management comprises a variety of individual sub-processes. It starts as early as clinical monitoring, this being the first time when data are checked for plausibility and accuracy, and clarified and rectified if necessary. (As a matter of fact, data management begins even earlier, i.e. when the CRF, the tool for recording data at the site, is drawn up. Whatever is missed at this stage will directly impact data management. However, 'common' understanding is that data management starts when data, i.e. CRF data, laboratory results etc. are transferred from the study site to the location where data management is performed.) Various ways exist to transfer data. The easiest way is that the monitor retrieves the original CRFs (hard-copies) from the investigational site. Alternatively, data may be transmitted by fax, electronic media or directly via the Internet.

Before analysis, it should be ensured that all CRFs are present and contain valid data. Thus, CRFs must be checked for completeness, plausibility and accuracy. Missing or implausible data must be identified, clarified or corrected. These clarifications are usually documented on so-called ‘data query sheets’ which become part of the respective CRFs. The query sheets are also commonly referred to as ‘data clarification forms’, ‘data request forms’, ‘query forms’, ‘data discrepancy forms’, etc.

Only valid CRF data will lead to reliable data in the database. However, prior to analysis, the entries in the database must be ‘cleaned’ as well. This step entails a multitude of data transformations: for example, ECGs, scans or other diagnostic tests must be converted into electronic data, implausible data must be identified and corrected as necessary, and discrepancies between first and second data entry must be identified, marked and clarified. Any database cleaning procedures must be finalized before the data are ready for statistical analysis.

The statistical analysis also includes various procedures in which data are transformed and converted. Statistical analysis programmes must be able to ‘read’ the database, data sets must be defined and marked, and outliers must be defined, identified and evaluated. Only then, the clinical data may be listed, statistically analysed and interpreted.

It is obvious that the multitude of processes followed for processing, cleaning, converting and correcting data is prone to incur a host of mistakes. At this stage of a clinical trial, it is essential to have a reliable quality management system in place, with quality control (QC) steps and audits, to assure the validity of the data. In view of the multiple processes in data management, the term ‘data management audit’ is a generic expression and encompasses numerous procedures to be checked. This chapter describes procedures for audits of databases, trial reports and related systems. However, this limitation should by no means suggest that there are no further audit aspects worth focusing on at this stage in a clinical trial.

## **2.1.1. Database audit**

### **2.1.1.1. Planning and preparation**

Like in all other audits, database audits require careful preparation. First, the audit must be arranged with the responsible database manager. Ideally, the person responsible for the data editing and/or programming should also be available for queries during the audit. In most cases, the date of database lock following the audit is a milestone in the project plan. The audit start date is calculated using this milestone date, taking into consideration the time required for conducting the database audit plus time for any required follow-up activities, to ensure that the database can be locked at the projected point in time.

Database locking is usually a two-step process. The first step is often referred to as ‘soft lock’ or ‘database freeze’ and occurs after all data cleaning, validation and QC activities have been finalized. The second step is

called ‘hard lock’ or ‘database lock’. At this stage, the database is handed over to statistics for data analysis and the data can be unblinded (in case of a blinded study). Audits of the database are conducted between ‘soft lock’ and ‘hard lock’ (‘freeze’ and ‘lock’) of the database.

Traditionally, database audits are performed under the maximum time pressure. Thorough planning – paired with flexibility – is essential.

Prior to the database audit, the auditor should receive the following documents related to the trial and the database:

- Study protocol including all protocol amendments, CRF, data management plan, statistical analysis plan.
- Annotated CRF, indicating the designation and names of CRF fields within the database to help the auditor identify the variables correctly.
- List of coding dictionaries employed in the trial (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Affairs (MedDRA), World Health Organisation Adverse Reaction Terminology (WHO-ART), WHO Drug Dictionary (WHO-DD)).
- List of the laboratory units used in the trial and possible conversions of units.
- List of ‘self-evident’ corrections performed by data management personnel. The list should include all corrections of obvious errors in the CRF that may be made by data management personnel without prior authorization by the investigator.
- List of all electronic and manual plausibility checks. It is recommended that this list be compared to the CRF as part of the audit to get a better understanding of the nature and adequacy of the checks.
- Standard Operating Procedures (SOPs) of all procedures related to data management.

Prior to the audit, the auditor, data manager and the responsible member of the clinical team should agree on an acceptable error rate for comparison of subject data listings with original CRF entries (for details see section 3.2 of this chapter). It is recommended to weigh the variables, e.g. to distinguish between primary and secondary variables to determine the sample size of the variables to be audited) and to define error rates based on this distinction. However, the definition of acceptable error rates does only make sense, if, at the same time, the consequences and corrective actions that apply in case acceptable error rates are exceeded are specified.

It should be recognized that acceptable error rates and audit sample size are interconnected and cannot be treated independently. Details are discussed in subsequent sections of this chapter.

#### **2.1.1.2. Audit conduct**

A database audit will make sense and be effective only, if it is conducted after the database has been cleaned and locked. Auditing a database that is still subject to change is similar to trying to hit a moving target. In most commercially available databases data can only be printed out after