ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)

Auditing Guide

This Auditing Guide has been developed and updated by APIC/CEFIC. You may use this for your internal auditing purpose but for the purpose of a Third Party Audit, please note that only APIC Certified Auditors are authorised to perform an official APIC Audit that is coordinated by the API Compliance Institute. While efforts have been made to assure the accuracy APIC/CEFIC cannot be held liable for any errors or omissions. You are not allowed to delete this disclaimer when using this template.

Content

1. Acknowledgements

This document was originally prepared by a group of experts within CEFIC / APIC. We thank them for their work and efforts spent as well as for their kindly co-operation, intensive discussions and fruitful comments:

Eva Lindqvist (AstraZeneca)

Lothar Hartmann (Hoffmann-La Roche)

Robert Hopkins (GlaxoWellcome)

Henri Leblanc (Rhodia)

Jörg Sachse (K + S Aktiengesellschaft)

Giancarlo Scuderi (retired, former Bracco)

Willy Verhaegen (Omnichem)

Frank Zimmermann (retired, former Knoll AG)

It has now been revised by the following CEFIC/APIC Quality Working Group Members and approved by CEFIC/APIC Executive Committee to bring it in line with the APIC Audit Programme:

- Tom Buggy, DSM Anti-Infectives
- Charlotte Hemmingsen formerly of Alpharma
- Anthony Storey, Pfizer
- and APIC Quality Working Group Members

2. Introduction

An audit performed by a well trained and thoroughly prepared auditor can be highly beneficial by identifying areas for genuine improvement.

The Pharmaceutical Industry has to deal with an ever increasing audit requirement as part of implementing European Directives that require periodic audits as part of Supplier Qualification, but also with different kinds of audits, other than GMP that cover, safety, health, environmental and financial aspects. Auditees may become stressed with overload and the potential advantages of audits are often going to be lost.

An audit should not to be seen as interrogation with the auditee as permanent loser, it is a comparison of what is laid down to what is in place. It is management's responsibility to initiate the necessary actions: either adoption of procedures and standards or taking corrective actions.

Inadequate training and/or preparation of an auditor can results in a lack of effectiveness, a miss of systematic approach and a demonstration of poor GMP knowledge during an audit. A number of supplier driven audits have led to a poor assessment by incompetent auditors.

The APIC Audit Programme is designed to ensure that effective, independent audits are performed by Certified Auditors and this Guidance Document is used as a key reference to provide advice on effective auditing and some of the tools used by APIC Certified Auditors, for example the Aide Memoire to ICH Q7 and the Audit Report Template.

For the purpose of this guide it is appropriate to make a distinction between an “audit” and an “inspection”. The term “inspection” usually implies to visits by regulatory authorities, who assess the compliance status with the requirements and have the potential for leading to regulatory or legal sanctions. In contrast the term “audit” is used in the context of a review by industry personnel with the objective of not only monitoring compliance but also identifying areas for improvement to the benefit of the business.

The purpose of this document is to provide expert guidance in best practice of conducting audits and for the implementation and maintenance of an effective audit system. In this regard the guide should be read in conjunction with ICH Q7 ”GMPs for APIs” and ”ICH Q10 Quality Management Systems”.

This guidance is written by experienced industry auditors. It is addressed to all involved in conducting and hosting audits/inspections. This guidance should make both parties (auditee and auditors) aware of potential conflicts and concerns and how to avoid/overcome them. It aims to set standards and provide awareness of the importance of audits/inspection in order to ensure a successful outcome. It is a powerful improvement tool in the hands of experts. Good auditors and hosts are required to be professional.

3. Glossary

Active Pharmaceutical Ingredient (API)
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Aide Mémoire
Document supporting the auditor(s) to conduct a structured audit.

Audit
A systematic, independent and documented process for obtaining evidence and evaluating it objectively to determine the extent to which criteria are fulfilled.

Auditee
Persons from an organisation or organisational unit being audited.

Auditor
A person with the competence to conduct an audit.

Audit Team
One or more auditors conducting an audit.

Audit Unit
An organisation or organisational unit (e.g. departments, plants, sites) to be audited.

Communication
Is a process of exchanging information between two or more persons. Communication can be verbal and/or non-verbal.

Competence
The demonstrated ability to apply knowledge and skills.

Compliance, GMP
Applying to national/international GMP regulations.

Compliance, regulatory
Applying to statements made in the organisations own documents submitted to the authorities.

Critical Quality Attribute (CQA):
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Process Parameter:
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Manufacture
All operations of receipt of materials, production, packaging, repackaging, labelling, re-labelling, quality control, release, storage, and distribution of APIs and related controls.

Material
A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

Outsourcing
Activity (laboratory, production, service) that is executed by another company on behalf of the original manufacturer.

Process
Set of inter-related or interacting activities which transforms inputs into outputs.

Quality Manual
Key document specifying the Quality Management System of an organisation.

Quality Unit(s)
One or more organisational units independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation.

Quality Management System
A management system to direct and control an organisation with regard to quality.

Questionnaire
Document asking for specific information.

Senior Management
Management that is not involved in the day-to-day business, but is in a position to implement changes or improvements.

Supplier
An organisation or a person that provides a product.

4. Scope

This document intends to provide expert guidance to the Pharmaceutical Industry for the implementation and maintenance of an effective quality audit system.

It is obvious that consistent standards for auditing will provide the following benefits to the industry:

- Effective assessment of GMP Compliance
- Reduced costs
- Improved performance
- Facilitating harmonised guidelines for auditing
- Increased external confidence
- Inspection readiness
- Trouble free operation.

Following this document will provide the current "state of the art" in pharmaceutical auditing.

5. Legal Requirements

The amended EU directives for Human and Veterinary Medicinal Products require the Manufacturing Authorisation Holders for Human and Veterinary Medicinal Products to ensure that all Active Pharmaceutical Ingredients used in the manufacture of Medicinal Products comply with the amended EU Directives 2004/27, 28 /EC.

Periodic audits done by or on behalf of the Manufacturing Authorisation Holder are expected as part of Supplier Qualification. The Qualified Person (QP) must prepare a declaration for licence submissions and renewals and ensure batches released to market only contain APIs manufactured as per ICH Q7.

Audits done directly by the Manufacturing or Marketing Authorised Holders are Second Party Audits where there is a Customer /Supplier relationship.

Audits done on behalf of the Manufacturing or Marketing Authorisation Holder by an independent body are Third Party Audits (refer to the APIC Audit Programme Document for further guidance).

http://www.apic.cefic.org/publications/publications.html

Companies should also have their own Internal Audit Programme as part of their Quality System (First Party Audits).

Internal audits or Self-inspections are also expected by the FDA,

6. Auditing

6.1 Audit types

6.1.1 General Considerations

The quality audit has been defined in a number of ways e.g. “An independent and formal review to determine the degree to which processes/products conform to standards set forth for them”, or “A systematic and independent examination to determine whether activities and related results comply with planned arrangements, and whether these arrangements are implemented effectively and are suitable to achieve the desired objectives”.

Whatever emphasis is used, the quality audit is a key management tool for monitoring the suitability of a company’s quality management system and in driving continuous improvement leading to GMP compliance and inspection readiness.

It may be appropriate to combine GMP / quality management system audits with safety, health and environmental (SHE) audits in order to reduce the overall number of audits performed. However, before the decision to combine these audits, careful consideration in order to derive maximum benefit is needed.

6.1.2 Audits Classification

From an API manufacturer’s point of view perhaps the most obvious distinction between audits is whether they are internal audits (a form of independent self assessment) or external audits (as may be performed on a critical raw material supplier).

6.1.2.1 Internal Audits

These may be conveniently subdivided into ‘local’ audits of individual plants and departments or projects, or ‘corporate’ audits performed by a central auditing group in order to assess conformance with corporate policies and standards.

These audits are likely to be structured to systematically provide in-depth knowledge of the effectiveness of the quality management system over the defined period of time. It is an internal check against internal, and where appropriate external, specified requirements reflecting the legal situation.

6.1.2.2 External Audits

By their very nature external audits performed on suppliers and/or contractors are checks against unknown environments of a product or service. They should evaluate if the GMP compliance status of the supplier is suitable for its intended purpose. Such

audits should not intend to impose customer standards on suppliers. These audits tend to be broader in scope, dipping into greater detail where problems are suspected. External audits are characterised as a check against the relevant international and/or local requirements given by the authorities. Other demanded standards (e.g. internal) are subject to discussion with the auditee.

External audits may be further subdivided with regard to their focus. While the search for evidence of an effective quality management system is a common goal, the level of required GMP may differ depending upon the criticality of the material and/or service (e.g. API, raw and/or packaging material, subcontracted registered intermediates).

Audits may also be used to approve (and/or qualify) suppliers and contractors. On-site auditing is recommended for suppliers of key services, critical raw materials, and contractors used for outsourced manufacture of API or intermediates.

Although auditing should focus upon suppliers of critical materials and services this need not be the only means of determining compliance. Alternative means of assessing compliance include responses to questionnaire, historical performance (including statistical evaluation of available data) and compliance history, reputation, third party certification, successful authority inspections, etc.

6.1.3 Justification

Audits may be conducted for a variety of reasons.

- As part of the Manufacturing Authorisation Holder evaluation to support a QP declaration of compliance to ICH Q7 for the API used as a Starting Material in the manufacture of Human or Veterinary Medicinal Products.
- As part of Supplier Qualification, a Pre-approval audit may be necessary
- '***Start up'*** audits would review the adequacy of new facilities and/or manufacturing processes prior to full scale production.
- As part of a periodic supplier evaluation, a ***'follow up'*** audit would be scheduled to monitor and ensure an adequate level of compliance is being maintained.
- A ***'for cause'*** audit may be performed to investigate a specific quality failure or process deviation and/or to prepare for a regulatory inspection.

Other audit drivers may include the desire to support the content of an approved list of suppliers and/or a reduced incoming materials testing programme.

6.2 Organisational Aspects

The level of organisational activity required to ensure the success of an audit, whether performed internally or externally should not be underestimated.

6.2.1 Company Policy

The general nature of an audit should be to identify the discrepancies between what is in place compared with what should be in place (i.e. specified requirements) rather than imposing solutions.

There should be demonstrable commitment by senior management to the use of auditing as a tool for continuous improvement and to ensure regulatory compliance. This should be reflected in adequate resourcing and, in the case of the internal quality audit programme, visible support for the timely progressing of agreed corrective actions. Senior management authorisation of the forward audit schedule usually ensures close adherence to the audit programme by all concerned.

It is a major concern if management uses audits for assessing or grading (e.g. salary) people. In this case it is likely the auditees will be defensive and not willing to co-operate, which is unacceptable, this will undermine the benefits of audits; auditees will feel themselves as examined by specialists (auditors) on areas they are not responsible to be at the state of the art. The consequence is an unproductive atmosphere and there could be attempts to hide the truth.

Audit-related activities from planning through implementation to effective follow-up (see chapter 6.3.6) should be formalised to ensure uniformity. This will involve combining GMP and Quality Management System audits in view of their complementary nature.

6.2.2 The Internal Audit Programme

To ensure effective use of time and available expertise it is essential to establish an agreed forward audit schedule covering at least 12 months. This should, however, be flexible enough to accommodate unanticipated events.

While unannounced audits may be theoretically appealing (and necessary in the case of suspected fraud), in practice pre-scheduled audits are less disruptive and more practical to ensure that relevant personnel and information are likely to be available.

The frequency and duration of audits needs to be carefully considered and this should be on a risk based approach.

Benefits may also be obtained by using different auditors, also from different sites and disciplines, for subsequent audits of the same area/activity to achieve synergy of

auditing expertise and experience. This may also be achieved by using external consultants.

6.2.3 Aspects Of External Audits

Visits by external auditors provide useful independent feedback on the effectiveness of an organisation's own internal quality audit function and quality management systems.

Audits of external suppliers and contractors are likely to be less frequent, but of longer duration than most internal audits. It is recommended that these audits are restricted to a maximum of two days due to disruptions, limited resources and costs to the auditee. For an evaluation of an API supplier by a Manufacturing Authorisation Holder a frequency period of two to three years is recommended by the European Authorities.

An API manufacturer may be inspected by regulatory authorities, audited by customers, or in certain circumstances audited by consultants undertaking Due Diligence activities. It is, therefore, advisable to define the company policy for managing external audits, detailing roles and responsibilities for those involved in preparing for, and hosting, such audits. In particular, it is important that staff are made aware of, and trained in, ways of responding to an external auditor's questioning techniques. Particularly in the case of regulatory inspections, many companies operate a 'control room' activity which co-ordinates activities, forewarns areas about to be audited, and checks documentation prior to its presentation to the inspector.

It is recommended to set up a secrecy/confidentiality agreement(s) before the audit in order to avoid miss-understandings later on about what information can be used or distributed.

6.2.4 Hosting Audits

The effective management of audits performed by external parties (customers or Third Party Auditors or, inspections by regulatory authorities or certification bodies) is vitally important. Therefore additional organisational issues for consideration are as follows:

- Availability (and if necessary translations) of key documents
- Assembly of a 'task force' to co-ordinate preparations
- Composition, organisation and responsibilities of the host 'team'
- Domestic arrangements (settings) such as office space with ambient temperature, communications, avoiding interruptions (e.g. telephone), etc.
- Availability of key staff, and involvement of senior and/or top management (provide correct partner for discussions)
- Training of staff in what to expect, and how to respond to an auditor's questions
- Decide policy on accessibility to internal audit reports
- Identify restrictions (e.g. photographing, video taking, areas not assessable, etc.)

- Provide permanent escort to auditor; Organisation of an exit meeting with required attendance of representatives from senior/top management.

It is, therefore, advisable to have in place a written procedure detailing roles and responsibilities for those involved in preparing for, and hosting, such audits.

6.3 Steps in Managing the Audit

6.3.1 Introduction

To achieve its' objective efficiently and cost-effectively an audit should be thoroughly planned, carefully structured, systematically performed, faithfully reported, and remedial actions progressed to a timely and satisfactory conclusion. As with most issues involving people, clear and effective communication with the relevant stakeholders is essential if business benefits are to be maximised through strengthening all aspects of the customer/supplier relationship.

Issues for remedial action will be a prominent feature of the audit report. If these are ignored the audit will have incurred a significant failure (and lost opportunity) cost to both auditor and auditee.

6.3.2 Pre-audit Information

The collection, collation and analysis of relevant information is an essential pre-requisite for successfully planning a quality audit. It is important to clearly establish the reason for performing the audit (e.g. new supplier; outsourcing; defect/recall investigation; routine re-audit; remedial action follow-up; etc.) in order to determine the type, scope and specific objective(s) of the audit. There should also be a clear business benefit to justify the cost, to both auditor and auditee, of undertaking the audit. This may, for example, be to satisfy a regulatory requirement, or to gather information to justify reduced analytical testing upon future receipt of a raw material (Clarification: This in no way absolves the manufacturers (supplier and receiver) from performing all necessary tests prior to release and dispatch).

A major source of information is the pre-audit questionnaire which, if well constructed, sufficiently comprehensive and used in a timely manner, can be an extremely valuable tool if responses are analysed carefully (see template annex 1).

Experience of previously received product, particularly problem deliveries (in the case of a supplier audit), together with earlier audit reports (if they exist) can add value to the preparation for a quality audit.

6.3.3 Preparation

Dependant on the scope of the audit the audit team can be composed of one or more auditors. If special expertise is required the team can be expanded by the inclusion of (a) specialist(s). If there is more than one auditor a lead auditor should be assigned and responsibilities should be agreed. It is advisable to interchange auditors from time to time for a given area in internal audits. This will combine the benefits of a detailed understanding of the areas/activities with the broader expertise and experience of different auditors.

Contact with the auditee should be made well in advance of the audit to allow adequate time for the necessary arrangements to be made, and initial information gathering to take place.. A Primary Contact within the Quality Assurance department of the Auditee should be defined at the outset for a Customer or Third Party Audit and regulatory inspection. The lead auditor or Inspector will then be in direct communication to make the necessary arrangements and agree the agenda in advance of the audit.

When a pre-audit questionnaire (Annex 1) is used, and this is strongly advised, responses should be studied carefully by all relevant stakeholders, and clarification requested as appropriate. This will allow the audit proper to concentrate on areas of uncertainty and/or perceived weakness thereby saving time and reducing inconvenience, to the benefit of both auditor and auditee.

Previous audit reports are another valuable source of information. Similarly, discussing experiences, good and bad, with recipients (e.g. internal customers in the case of an internal audit; your raw materials testing laboratory in the case of an external raw materials supplier audit) can provide useful information such as batch/lot numbers for challenging traceability etc.

The agenda for the audit should be communicated to, and agreed with, the auditee. This could also identify key reference documents (e.g. GMP; Quality Manual, etc.) and relevant working documents such as checklist(s), etc. to be used during the audit.

The auditor should be aware of any sensitive issues, for example Highly Confidential information and, should any conflict arise during the audit, the auditor should take care to handle the issues in a way that will not jeopardise the relationship with the auditee.

6.3.4 Performing the Audit

The audit should commence with an opening meeting to introduce auditor(s) to relevant auditee staff and Senior Management Representatives (especially relevant for an external audit or inspection); review scope and objectives, and finalise and agree the agenda and timetable. The opening meeting also provides an opportunity to explain the audit rationale, clarify the audit plan, agree communication channels and clarify ambiguous replies in the pre-audit questionnaire.
In the case of an external audit the opening meeting also provides an ideal opportunity for the auditee to explain Company rules concerning e.g. safety, taking photographs,

confidentiality of information, taking samples, talking with operators, making recordings, etc.

The auditor should decide in advance whether to use a detailed checklist or (less detailed) 'Aide Mémoire' (see annex 2), or simply rely on memory and experience. If the former, then it is a courtesy to explain this approach to the auditee. The Aide Memoire has the advantage of maintaining focus by providing structure to the questioning sequence and ensuring that all listed issues are covered. However the auditors should feel free to spend more time on specific topics where compliance issues are becoming apparent and so should used the Aide Memoire as a guide from which the auditors can deviate if a concern arises over an issue not covered by the checklist.

During the audit it is usual to walk through relevant parts of the facility to observe the operation at first hand, to gather information, to assess the cleanliness and condition of facilities and the risk of potential contamination. Some auditors prefer to undertake a brief 'tour', following the introductory meeting, in order to familiarise themselves with the size and complexity of the operation and achieve a clearer understanding of workflow and relative location of different activities. They may subsequently re-visit relevant areas to review GMP/systems compliance in greater detail.

During the audit evidence of compliance, or otherwise, will be obtained through observation, questioning, examining documentation and records, and challenging issues of concern. All relevant observations should be recorded clearly and concisely together with supporting evidence. Concerns should be discussed with the auditee as they arise to avoid surprises in the Closing Meeting.

The closing meeting is particularly important since it allows the auditor (or audit team) to communicate the audit findings and conclusions in a logical and co-ordinated manner to the auditee's management. It is, therefore, useful to provide a simple agenda and a short written summary of observations. It is important to emphasise the good news as well as highlight the areas for improvement together with supporting evidence. Audit deficiencies should also be classified to highlight the priority for actions to the auditee and their Senior Management. The Audit Report Template (Appendix D) includes a Classification definition based on the EU GMP Inspection Report Format and this is used as standard in the APIC Audit Programme.
Deficiencies are classified as follows:-

1. Product Quality / Patient Safety Related deficiency (**Critical**)
2. Significant cGMP Deficiency but with no **direct impact** on Product Quality /Patient Safety (**Major**)
3. GMP deficiencies that are either considered to be minor isolated examples or there is insufficient information to classify them as Major (**Other**)

As stated above, the deficiencies should contain no surprises for the auditee, as all concerns should have been raised during the audit. The auditee should be given the opportunity to clarify and fully understand the evidence for the deficiencies. In this way there will be an acceptance of the findings and the auditee can then plan to fully address the audit findings rather than replay the audit.

While it is the auditors role to identify what needs to be achieved when a problem is identified, in the case of Second or Third Party Audits he/she should not be prescriptive in 'how' to achieve it, although advice may be offered, if specifically requested.

6.3.5 Reporting the Audit and Auditee Response

The single most important product of an audit is the audit report. It provides a record which identifies and may be useful for prioritising (e.g. Critical, Major, Other) areas for improvement. The audit report should be drafted, and the final version issued, as soon as possible after completion of the audit for reasons of both accuracy and effectiveness. Suggested timings are within a maximum of 3 weeks. It is recommended that a draft of the report be supplied to the auditee for comment and check on the factual accuracy and to avoid misunderstandings arising over observations and recommendations.

Confidentiality of internal audit reports are subject to company policy. These reports are normally not made available to external auditors and inspectors from regulatory authorities.

6.3.6 Follow Up Of Progress with Remedial Actions

The timely implementation of corrective actions, and verification of their effectiveness, is essential to the concept of continuous improvement.

The efficiency and comprehensiveness with which agreed remedial actions are progressed is often a good reflection of the auditee management's true commitment to quality. While minor remedial actions may be followed up at the next routine audit, progress with major issues should be reported within an agreed timeframe. It may also be necessary to re-audit to ensure that serious remedial action has been satisfactorily completed for Critical or Major deficiencies.

Failure of the auditee to actively progress major and/or serious actions should be referred to senior management (in both companies in the case of an external audit).

Responsibility for Follow Up and to decide timing of next audit lies with the customer or stakeholder responsible for initiating the audit and specifically with the QP of The Manufacturing Authorisation Holder for Human and Veterinary Medicinal Products in the case that the audit is done as part of ensuring effective GMP Compliance for Active Substances used in the manufacture of Medicinal Products in Europe.

6.3.7 Possible Audit Breakdown

The breakdown of an audit should be an exceptionally rare occurrence. However, it may be the result of poor planning/preparation, failure to clearly define and agree scope and objectives, an inadequately trained auditor or one lacking the appropriate personal characteristics, poor communication before and during the audit; and/or lack of

commitment/co-operation/understanding on the part of the auditee. In such circumstances the scope for action to improve the situation is usually limited to either trying to identify and resolve the root cause (usually with the help of senior management) and endeavouring to continue with the audit or, as a final resort, to abort the audit.

6.4 Content of An Audit

However skilled the auditor, it is most unlikely that one audit will encompass every aspect affecting quality. A number of factors have to be taken into account before deciding on the scope, nature and content of an audit.

The selection starts with the determination of the major areas the audit should focus on: production, laboratories (both Quality Control and In-Process Control), storage (raw materials, intermediates, APIs and packaging), transport and distribution, engineering and maintenance, development and Quality Assurance.

The next decision to be made is if the nature of the audit is more product related (checking specific SOPs , batch records, reprocessing operations, definition of API Starting material etc.) or system related (handling of deviation/investigation procedures, change control procedures, checking interfaces between different departments etc.) or a mixture of both.

For API Manufacturers, distributors, traders or brokers, the content itself, i.e. the GMP requirements the auditor(s) are going to evaluate and to check against, is ICH Q7 the GMPs for APIs. Furthermore an interpretation of these ICH guidelines is given in the CEFIC publication "How to do - interpretation to the Q7a document", which can be accessed on the Internet (http://apic.cefic.org/framecommunica.html).

In annex C (Aide Mémoire) a detailed listing of the content is provided. This Aide Mémoire is structured according to the ICH Q7 document and supports the auditor(s) on concentrating to the relevant items. Experience has shown that rigid adherence to a too detailed checklist can lead to possible overlooking of important issues.

As audits should assess the GMP compliance it is also important to mention that a check for regulatory compliance is essential for the company too. A comparison of the registered files (NDA, DMF, CEP) with the situation in the manufacturing facility may also be considered part of the audit.

Audits performed as part of an internal quality audit programme (which may range in scope from R&D through Manufacturing and QA to Shipping) should not necessarily be limited to review compliance with relevant GMP requirements, but also should encompass conformance to Quality Management System principles, if these are in place. Combining those two different audit approaches (GMP and QMS) will benefit in a better understanding of the overall situation and lead to synergies in form of saving time and resources.

6.5 Documentation

6.5.1 Principle

An effective communication supported by good documentation is regarded an essential element for the successful planning, performing and follow-up of an audit.

6.5.2 Types of Documentation

Before, during and after an audit different types of documents are utilised. The list given below may not be all-inclusive but consists at least of the major documents:

Before the Audit:

- Pre-audit documents
  These can be all kind of documents like old audit reports, agreed corrective actions, internal minutes, memos, credit applications, product specific information (e.g. chemical synthesis), internal company directives and guidelines, general information about the company to be audited (external), the ICH Q7 document and Cefic's "How to do - interpretation to the ICH Q7a document".
- Pre-Audit Questionnaire
  Document requesting general information for the preparation of the auditors.
  See annex 1
- Audit plan
  Gives a general overview of the audit units, the frequency in which the audit units ought to be audited and provides a summary of the audit units to be conducted within a year.
- Audit schedule
  Fixed dates at which the audit will take place for a pre-defined timeframe (usually a year). If not too complex, the Audit Plan and Audit Schedule can be combined to one document.
- Letter announcing/requesting the audit
  The auditee must be given the chance to organise himself. For this reason the auditor(s) should seek for an invitation well in advance of the planned/scheduled audit. This may be in form of a letter (mostly external) or memo (mostly internal) or even by e-mail.
- Audit agenda
  An agenda agreed between auditor(s) and auditee, defining the topics to be focused and/or audited units.
- Secrecy agreement
  It is advisable to sign a secrecy agreement for external audits (supplier, contractor). Most often the auditor will be taken into sensitive areas, where a knowledge transfer, caused by the auditor, could lead to competitive disadvantages.

During the Audit:

- Aide Mémoire
- See Annex 2
- Personal notes, see 6.5.3

After the Audit:

- Audit report, see 6.5.3 and annex 3
- Response to Audit Report
  The auditee should be given the opportunity to respond to the audit findings by how the observations will be dealt with, the time needed and indicating the responsible person. It also may be possible that the auditee disagrees with an observation in which case the auditee's management must take a decision. There is a Disagreement Resolution procedure within the APIC Audit Programme as this will be used for Independent Third Party Audits reported to the Qualified Person of the Manufacturing Authorisation Holder and the report may be shown to EU Member State Inspectors.
  The response to an audit and the audit report may be combined to one document as shown in annex 3
- Action list
  Resulting from the audit report it is helpful to implement a separate list of all actions and timelines in order to ensure proper follow up to the given commitments and having a rapid overview of the status of completed activities.
- Progress Report
  In case of long audit intervals or a significant number of serious observations the issuing of a Progress Report is recommended. A follow up meeting or audit should also be considered, if the status of compliance is insufficient.

6.5.3 Recommendations for compiling and handling the audit report

Observations made during an audit should be laid down in writing. In spite of the fact that an audit is a powerful tool there is some chance that the issued audit report can lead to misunderstandings and disturbances at the side of the auditees. In order to avoid surprises with the audit report there are some fundamentals that should be taken into account.

It starts with taking personal notes during the audit. It is essential and highly important that an auditor makes himself sufficient and detailed enough notes during the audit. It is necessary to take the time and when the auditor is by himself it has to be accepted that there are quiet moments while the auditor is writing down his comments and observations. Nothing is worse than incomplete notes from which later on when writing the report incorrect statements arise.

When writing down the observations the auditor must be able to trace back his findings to recognised guidelines (here: ICH Q7). It is insufficient to argue that “FDA or EMA has said…” (or any other regulatory body). The auditee must be confident that he does

not get confronted with the personal opinion of the auditor, but with objective recommendations against those he is compared with.

When writing the audit report it might be useful to involve the auditee. Most often this is done by sending the auditee within three weeks the draft audit report to check factual accuracy and asking the auditee to respond. The corrective action plan for each observation should be submitted to the audit team in 30 calendar days or any other period agreed by both parties proposing corrective actions, responsibilities and time frames.

Internal Audit reports should not be shown to Third Parties such as customers, consultants or even inspectors. It is advisable to have a company procedure in place describing the restricted distribution of internal audit reports to avoid conflict situations during a Second or Third Party Audit.

Third Party Audit Reports of an API manufacturer may be inspected during an EU Member State Inspection of the Medicinal Product Manufacturer. The APIC Audit Programme contains a clause in the Audit Agreement where the Auditee, Auditors and Manufacturing Authorisation Holders agree to this in advance of the audit.

6.5.4. Classification of observations

During an audit the auditor will write down a number of observations which have significance. It is common and helpful to classify audit observations according to their importance and thus providing an orientation on urgent actions to be done for example, classifications used in the APIC Audit Programme are included in the Audit Report and are summarised in section 6.3.4.

6.5.5 Archiving

Audit reports as well as associated documents as listed in 6.5.2 need to be archived for the purpose of evaluating the compliance history at the time of a new audit or for informing senior management about status and developments in terms of compliance. It is thus necessary to retain such documents for a sufficient period of time. The time period of storage for these documents should be laid down in a written procedure by the company. As there is no official GMP requirement for the storage time of auditing documentation, in general, it should be at least 7 years unless otherwise justified. Third Party Audit Reports also should have a Validity Period and a maximum of three years is defined for APIC Audit Reports.
The auditing documentation does not necessarily be archived by paper. All other technical options such as micro-film, CD or electronically on computer servers are acceptable as long it is ensured that the files can be accessed over the retention period.

6.6 Qualification and attributes of auditors

Auditors should be qualified by education, training and experience in auditing techniques. Incorrect statements or interpretations of regulations can be extremely costly and prejudicial to a company. Therefore the auditor should be fully knowledgeable in the understanding and interpretation of applicable regulations. They should also have excellent communication skills as it is of paramount importance, not only that all observations are well understood, but also that no conflict situations arise in the course of the audit.

6.6.1 Training, Experience, Education, Background

6.6.1.1 Education

Because of the nature of API manufacture, it is recommended for the auditors to have a good educational knowledge of chemistry. Qualifications as Pharmacist, Medical Doctor, Chemical Engineer, graduate or Ph.D. in Chemistry, Biology or related fields as Agrochemistry etc., are appropriate. A good understanding of biochemistry and of analytical techniques and practices is a definite advantage.

ISO 10011, Part 2 requires at a minimum secondary education. Because GMP audits may include the in depth review of complex systems/techniques as water systems, impurity profiles, verification of compliance with notified information etc. a higher requirement is given in this guide, corresponding to a minimum of secondary education.

With the exception of Pharmacists whose university courses may include modules on GMP Regulations, a good knowledge of applicable regulations is usually obtained through training and experience.

6.6.1.2 Training

Training should start with collecting, reading and understanding the applicable GMP (ICH Q7) and other related reference and guidance documents.

It is sound practice to participate at regular intervals (e.g. once a year) to recognised seminars and conferences where regulations and trends are explained and interpreted.

The auditors should also be trained in auditing techniques including planning, organising, questioning, communicating and reporting. For example, in the APIC Audit Programme, a five day training programme combining GMP knowledge and training in auditing techniques is a pre-requisite for APIC Auditor Certification.

6.6.1.3 Experience

A career within the Pharmaceutical Industry for example in Production, Technical Support, Quality Control or Quality Assurance may contribute to the appropriate

qualification by experience. ISO 10011 requires a minimum of 4 years of practical workplace experience of which 2 year in QA activities.

Experience is also obtained through participation to audits, either as auditee, or as co-auditor. ISO 10011 requires at a minimum participation to four audits for at least 20 working hours.

6.6.2 Mental Stability

Because of the need to obtain the proper information and because of his educational role, the auditor should be able to prevent any conflict situation and to create a positive, constructive environment. The audit should always be conducted in an amiable atmosphere, with tact, honesty, diplomacy and persuasiveness. Therefore the auditor should have a very stable character, be able to restrain himself from emotional, aggressive or discouraging declarations in the course of the audit.

During the audit, the auditor role is to collect the information in an objective manner, keeping the auditee informed as the audit proceeds.
In this way serious misunderstandings in the Closing Meeting can be avoided..
In the Closing Meeting or review of Audit Report phase, the auditor should resist to any pressure from the auditee to revise or reclassify the audit findings unless of course a clearly explained error in the accuracy of the findings has occurred and is accepted by the Lead Auditor.

6.6.3 Conflict Situations, Compatibility

Whenever a conflict situation arises, the auditor should never resort to threats, intimidation or strong arm tactics. In most cases, a calm, patient, sympathetic or persuasive attitude will overcome the persons reluctance or hostility.

If the above fails, further actions will depend on the nature of the audit.

- ***Audit of an aggressive supplier***
  Appropriate actions may include notification of senior management of the supplier, directly or, as appropriate, through the auditors' purchasing department.

- ***Audit of one of your facilities***
  Information provided with justification to senior plant management or corporate management of the situation, mentioning the possibility to discontinue the audit if no satisfactory solution can be found.

- ***Audit by a customer***
  These audits are usually witnessed through the local sales agents whose role is also to smoothen any conflict situation when these arise and who may notify the auditors hierarchy or commercial departments whenever such situations arise.

- ***Audit by an authority***
  This situation should never arise as authorities are under strict behavioural instructions. In the event of professional misconduct, notification of their Inspectorate may be appropriate by Senior Management of the Auditee, usually the Corporate Quality Director.

6.6.4 Social Competence

All auditors (lead auditors and co-auditors) should exhibit a proper social behaviour to ensure no conflict situations or improper attitudes arise in the course of the audit. Auditors should realise the auditees may be stressed and feel challenged or undermined aggressed by the attitude, remarks and comments of the auditors.

There are no educational requirements for social competence. However, management should assess the social behaviour of candidates before nomination as auditor.

Unsociable or unstable individuals do not qualify as auditor.

6.6.5 Communications Skills

Because of the key role of an audit for the company, it is of utmost importance that all remarks are well understood and accepted. Therefore, the auditor should, at any time, explain in a didactic manner, why he believes a situation is not acceptable or should be improved.

Training in communication skills is a definite requirement for an auditor.

It is beneficial if one of the auditors is fluent in the language of the auditee. If this is not possible, then a responsible individual (e.g. the quality assurance manager) should be designated to translate and explain the questions, comments and remarks of the auditor as well as the responses of the auditee.

The auditors should try to assess whether or not the translator provides a faithful translation.

6.6.6 Flexibility

The GMP reference is given by the ICH Q7 document which is by nature more a « what to do » rather than a « how to do » guide. Therefore alternate approaches to reach these standards are permissible, provided they result in the same level of assurance for product quality.

The auditor should not impose his solution to a given problem and be receptive to alternate solutions.

An auditor should also not expect that all functions are available all the time at the time he dictates. Whenever appropriate, he should outline who and when he expects to see those, in order to create minimum disruption to the auditee's facilities.

6.6.7 Requirements for Lead Auditor

The lead auditor takes a key role in the auditing process with a number of tasks and responsibilities. He should:

- Inform the auditees of the purpose of the audit and agree the audit agenda,
- ensure that the agreed-upon audit agenda is followed,
- co-ordinate the activities of the other auditors, in particular, when the auditing party subdivides into distinct parties,
- ensure consistency throughout the audit, e.g. prevent non-productive nick-picking side discussions,
- consolidate all findings,
- present the audit findings and classification to senior management at the conclusion of the audit.

Because of the possible major consequences of his decisions, the lead auditors must be extremely competent in GMP standards and auditing techniques. As a minimum, he/she should :

- Be independent from production or economic constraints in his role as auditor
- Be recognised as having the required competence by senior management
- Have the required authority to take hard decisions if required by the findings of the audit (in-house audits only)
- Be independent of the company being audited or the requesting company in the case of a Third Party Audit
- Be fully accountable for his decisions
- Have been active in a GMP related area for a minimum of two years
- Have participated in at least three complete GMP audits as Co-auditor.

6.6.8 Assessment of Auditor Performance

Excessive auditors can cost companies very large amounts of needless spent money, whereas lax auditors may quickly lose all alleged financial savings by adverse findings by the authorities, or worse, public health issues due to real GMP deficiencies.

Therefore it is important that senior management has the tools to assess the auditor's performance. In large firms, this can be achieved through peer review. In smaller firms, the only possibility is often by the use of well recognised consultants who will provide an independent assessment of the firms' compliance situation, and hence, indirectly, of the auditors performance.

The auditor's performance can also be assessed by comparing his own findings by those of an independent auditor (e.g. consultant, authority or customer) and by assessing the firm's compliance record.

ISO 10011 recommends that an evaluation panel periodically reviews auditor performance, taking into account audit programme management's assessment of performance. As an example, a standard feedback form on audit preparation / auditor performance is included in The APIC Audit Programme Document and is used to review effectiveness of audit programme and auditor performance.

6.6.9 Certification for Auditors

Whereas ISO certification of auditors is possible in some countries, (for details see ISO-10011 Part 2, annex B2) this is not generally the case for GMP auditors.

Companies should have an internal scheme setting the criteria to qualify as auditor and to maintain this qualification status.

Typically this would be :

- Active involvement in a GMP related activity preferably for a minimum of two years
- Have participated in at least three audits as auditee
- Have followed an auditor training programme for example the APIC Certified Auditor Training course that is organised by the API Compliance Institute
- Conducts at least one audit per year

7 Benefits

Auditing is no goal in itself. Auditing in the pharmaceutical sector serves two different categories: regulatory compliance and business needs.

Whilst there is usually low influence on regulatory inspections, audits should be seen as management tool to assess company's in-house quality management system. Internal as well as external auditing can help to achieve this goal.

The major benefits of an effective audit system can be summarised as follows:

- Managing quality management system
- Detecting in advance weak points, through identification of unsatisfactory trends or situations
- Preventing quality failures, on the basis of quality data reviewing
- Informing Senior Management about quality level of facilities and/or operations

Standardising audits will optimise the output, the quality level of audits will increase (and therefore the quality of products and services) which will finally lead to a continuous improvement loop.

The auditee will understand that audits are not created to control and criticise his work, but will improve the company's performance. This will lead to a higher acceptance of the audits. He will see audits as a chance to educate and improve his knowledge in terms of quality related aspects.

Combining audits of quality, safety and environmental matters will reduce the number of audits significantly which will give a greater acceptance to the auditee and will save him time. Additional benefits can be achieved by pooling audits for example Shared Third Party Audits.

By establishing a high quality audit system throughout the industry the level of compliance will increase. Mutual confidence building and an improved relationship between the partners will be the result of these efforts.

8. References

1. ICH Q7 "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", November 2000
   published in EU: CPMP/ICH/1935/00, December 2000
   published in US: Federal Register, Vol. 66, No. 186, September 2001
2. CEFIC/APIC “How to do” Document, Interpretation of the ICH Q7a Guide, June 2002

http://www.apic.cefic.org/pub/How%20to%20do%20-%20ICH%20Q7a_Nov2006.pdf

3. CEFIC/APIC Quality Management System for Active Pharmaceutical Ingredients Manufacturers (September 2005)

http://www.apic.cefic.org/pub/191005_QMS%20for%20APIs%20Final.pdf

4. EN ISO 9000: 2000: "Fundamentals and Vocabulary", December 2000
5. EN ISO 9001: 2000: "Quality Management Systems -Requirements", December 2000
6. ISO 9001: 2000 - CEFIC Guidelines for use by the Chemical Industry, March 2001
7. EN ISO 10011 Part 1: "Auditing", June 1992
8. EN ISO 10011 Part 2: "Qualification criteria for Quality System Auditors", June 1992
9. EN ISO 10011 Part 3: "Management of Audit Programmes", June 1992
10. WHO Technical Report Series, No. 823: "Provisional guidelines on the Inspection of Pharmaceutical Manufacturers", 1992
11. PQG: "Pharmaceutical Auditing", Monograph, 1992 Institute of Quality assurance
12. IPEC: "Good Manufacturing Practices Audit Guideline for Bulk Pharmaceutical Excipients", November 1998
13. ICH Q10 “Pharmaceutical Quality System” step 3, May 2007
14. Eudralex Volume 4 “Medicinal Products for Human and Veterinary Use: Good Manaufacturing Practice” Mar 2007

9 Appendices

Annex 1 : Customer Questionnaire
Annex 2: Aide Memoire
Annex 3: Audit Report (template)