Auditing the microbiology laboratory

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21.1 Introduction

The optimal way to maintain good standards of quality across the microbiological function is through conducting audits. Audits can apply to the laboratory or to associate activities like the activity of sampling. Audits can include those from regulators, accrediting bodies, potential or existing external customers and from the internal quality team. They may be experienced microbiologists, quality system experts or non-microbiologists. Given the wide scope of the subject matter, this chapter is focused on the expectations surrounding an internal audit of the microbiology laboratory. An important aspect of audits, not addressed here, is with the microbiologist going into the process area to assess contamination risks and hygiene practices. The various chapters in this book provide ample material that can be drawn upon by the pharmaceutical microbiologist when investigating production processes and cleanroom activities.

Auditing is a part of Quality Management (which, in turn, is a component of Good Manufacturing Practice). Quality Management is a set of principles, many of which are captured in the ISO 9000 series of quality standards [1]. ISO 9000 captures definitions and terminology relating to quality systems and also links to ISO 9001, which details the actual requirements of a quality system [2]. The ISO standards apply across a range of industries and, whilst useful as an audit tool in terms of structuring an audit, they are not sufficiently process or laboratory specific to be used without additional microbiological knowledge.

There are varying definitions of an audit. Here it is defined as a systematic and independent examination to determine whether quality activities and related results comply with planned arrangements. In addition, the audit assesses whether these arrangements are implemented effectively and are, in fact, suitable to achieve objectives.

According to Martin [3], the key elements of an audit are:

- That it is systematic,
- That it is conducted by someone independent of the operations,
- That the audit be documented,
- That the audit findings be evidenced based,
- That the auditor evaluates the findings,
- That the auditor makes a decision regarding the extent that the audit criteria have been fulfilled.

Undertaking audits is a regulatory expectation, and the process of carrying out periodic audits is in itself an essential part of preparing for regulatory inspections. With this regard, auditing a microbiology laboratory follows the same process as auditing any other

Pharmaceutical Microbiology. http://dx.doi.org/10.1016/B978-0-08-100022-9.00021-9

quality functions. However, to be completely effective, the task requires knowledge of the area being examined—in this case microbiology—on the part of the auditor [4].

This chapter outlines the essential elements for conducting an audit for the microbiology laboratory and features some of the important areas which the auditor should focus on. These areas include:

- Media preparation and quality control,
- Maintenance of microbiological cultures,
- Maintenance of laboratory equipment,
- Laboratory layout and operation,
- Training of personnel,
- Documentation,
- Maintenance of laboratory records,
- Interpretation of assay results.

21.2 Quality audits

A system for self-inspection (alternatively called an "internal audit" to distinguish the audit from a supplier audit) must be in place. Internal audits should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice (GMP), as well as what it is termed Good Control Laboratory Practice (GCLP) within Europe and Good Laboratory Practice elsewhere. Internal audits should be conducted in an independent and detailed way by designated competent persons.

There are broadly two types of audits that could apply to a laboratory: the compliance audit and the quality audit. A compliance audit is designed to determine whether or not specific activities have been performed according to documented procedures (SOPs). In a compliance audit, the SOPs are not questioned. The objective is to determine compliance with the rules, and the outcome is usually binary, either passed or failed.

However, a good GMP system will not function or improve without adequate audits and reviews. Here the quality audit introduces an element of questioning. A quality audit focuses on identifying the underlying cause of quality problems. Such audits can be very effective in identifying testing practices that may not be as effective as they could be. Whichever class of audit is agreed upon, audits should be performed regularly and systematically, to ensure the laboratory is meeting its objectives [5].

There should be a schedule for carrying out audits, with different activities possibly requiring inspection at different frequencies. An audit should not be conducted with the aim of revealing defects or irregularities. The appropriate philosophy is that the audit sets out to establish facts rather than simply finding faults. Audits often indicate necessary improvement and corrective actions, but they must also determine if processes are effective and that responsibilities have been correctly assigned. The emphasis should be on process improvement and enhancing customer satisfaction.

The generic steps involved in an audit are [6]:

- Initiation,
- Scope,

- Frequency,
- Preparation,
- Review of documentation,
- The programme,
- Working documents,
- Execution,
- Opening meeting,
- Examination and evaluation,
- Collecting evidence,
- Observations,
- Close the meeting with the auditee,
- Report,
- Preparation,
- Content,
- Distribution,
- Completion,
- Report,
- Submission,
- Retention of the audit report.

The above can be simplified as PLAN–DO–CHECK–ACT.

21.3 Auditors and the audit process

Auditors should be knowledgeable of microbiology and be trained specifically as auditors. Auditors should have complete independence of the functions they are auditing. In addition to understanding the processes, strong interpersonal skills are critical to the success of an auditor and the audit he or she is performing. There is a natural defensiveness which occurs on the part of the auditee, and an audit can be an emotional experience. Good auditors are persistent without being relentless; ensure they have their questions answered and thoroughly understand a situation before they evaluate what they have seen and heard.

Some the interpersonal skills required by auditors include:

- Objectivity,
- Tact,
- Fairness,
- Not having any preconceptions,
- Thoroughness,
- Persistence,
- Technical knowledge,
- Strong questioning and interviewing skills,
- Detailed understanding of Good Manufacturing Practices and clauses,
- Confidentiality.

As well as looking for negative points, auditors should highlight positive aspects of the area visited.

In terms of approaching the audit, one generalized approach is:

(a) Initiation

The audit must be initiated by one party, and the two parties (auditor and auditee) must agree to the audit taking place and to the schedule.

(b) Scope

The activities that are to be included in the audit must be decided in advance of the audit by the auditor.

(c) Frequency

The frequency of the audit (how often an area is to be audited) must be determined. In one sense, this will help to determine the scope, for if an area is subject to many audits (such as internal monthly audits) then this may lead to mini-audits focusing on defined parts of the larger area taking place rather than one large audit of an entire facility.

(d) Preparation

Before an audit is undertaken, the auditor must prepare for the audit and understand the function of the area to be audited and its key operations. This includes familiarity with the facility, understanding the type of product produced and how it is organized by personnel and function. This is sometimes referred to as the audit task plan.

(e) Review of documentation

Often the auditor will read documents pertaining to the area to be audited in advance. This may include, depending upon the scope of the audit, the Quality Policy or Site Master File.

(f) The programme

The auditor should map out the programme for the audit in advance. This may include considering questions like: What will be covered? What needs to be looked at? What should be witnessed? Which key documents will be reviewed?

In doing so the auditor will decide upon how the audit will be executed.

(g) Opening meeting

Audits begin with a meeting. The meeting will consist of the auditor and representatives of the area to be audited. At the meeting, the auditor will outline the scope for the audit.

(h) The visit

An "audit" is typically divided into two key steps: visiting the area(s) subject to the audit and documentation review (see below). The visit consists of the auditor being escorted around the area. During this phase, the auditor will examine the area (noting things like fabric), watch activities being carried out, ask questions of staff working in the area, and check records. The auditor may ask for other documents relating to the activities to be reviewed later.

It is a good idea for the auditor to use a checklist. The auditor should take note of things which do not seem correct. These will later be classified into observations and into non-compliances.

(i) Documentation review

Either during the facility tour or at the end of the tour, the auditor will review any requested records. These may include Standard Operating Procedures and training records. Documentation represents an important part of the audit.

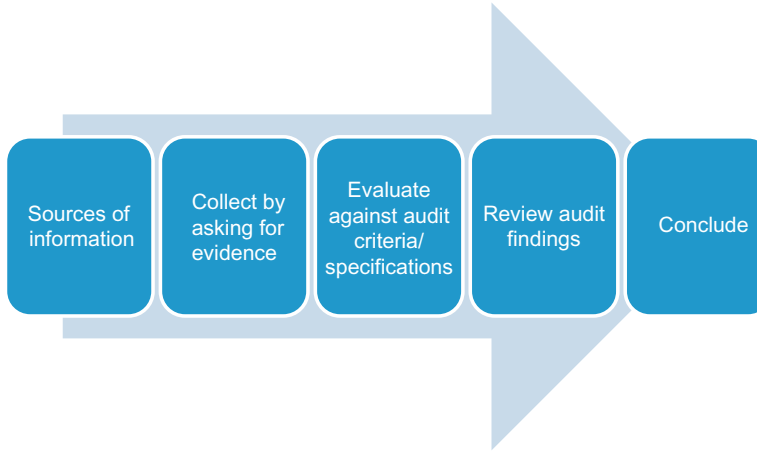

Figure 21.1 Simplified audit evidence collection process.

With the visit and documentation review, a useful approach is outlined in Figure 21.1.

(j) Close the meeting with the auditee

At the end of the audit, the auditor will prepare the findings. These must be presented to the auditee in a closing or wrap-up meeting. The auditor will convey the importance of the findings and make reference to regulatory documentation where necessary. It is important that anything to be covered in the final report is included in the closing meeting, for the report should not contain non-compliances not raised with the facility staff at the end of the audit.

(k) Report

Shortly after the completion of the audit, the auditor must write a report. The report should be held by the auditor's company. Either the full report or, more normal for an external audit, a summary report, is sent to the manager of the area which has been audited. Where non-conformities have been noted, the area which has been audited should respond to the audit findings within a short time period (typically within 30 days). As appropriate, corrective and preventative actions should be set.

21.4 Auditing the microbiology laboratory

The above part of the chapter presented a general model of the audit process. This part of the chapter outlines some of the important aspects of the microbiology laboratory that should be assessed during an audit. The applicability of each topic will depend upon the remit of the laboratory.

21.4.1 Microbiology personnel

During the audit a question may be asked whether the laboratory has the correct number of appropriately trained staff. It is important that written procedures define the training of microbiological staff in both cGMPs and microbiological techniques. This

will extend to cleanroom entry and the taking of environmental monitoring samples, in addition to standard laboratory techniques. The laboratory should be able to present a training plan and procedure, together with training records for all staff.

21.4.2 Laboratory design and sample flow

In current cGMP guidelines, it is implicit that microbiology laboratories should be of an appropriate size to carry out all their functions. This needs to cover all aspects of sample handling and storage, dedicated test areas for different materials, media preparation, incubation, handling of microbial cultures and treatment and removal of bio-hazardous waste. Some aspects of work may take place in demarcated areas, such as the reading of environmental monitoring samples, endotoxin testing, and for the identification of microorganisms. Sterility testing must always be conducted within a purpose build test facility.

In addition to the design of the laboratory, auditors will expect to see a logical flow of samples through the testing process and adequate controls to protect the samples and activities from extraneous contamination. For example, the use of qualified unidirectional airflow cabinets and biological safety cabinets as measure to ensure contamination control.

21.4.3 Sample handling

Sample receipt, handling, storage and documentation will be scrutinized. A sample should be labeled with an identity, source of the sample, quantity, batch number or other distinctive code, date sample taken, and date sample received into the laboratory. Additional documentation may be available to define what tests are to be performed on the sample, storage conditions, timescale for test completion or other information. Many microbiological samples have strict storage conditions, and many will have expiration dates, and the audit will need to verify these. For example, water samples will need to be placed under refrigerated conditions a short while after sampling and will need to be tested within a defined period (measured in hours) after sampling. Sample handling will either be captured through paper records or via a computerized system.

21.4.4 Culture media

The quality of work undertaken in the microbiology laboratory depends on the quality of the culture media. Therefore, media preparation and quality control form essential elements. As with standard laboratory practice, for media, reagents, chemicals and so forth entering the microbiological laboratory, there needs to be in place procedures that define receipt, preparation, labeling, storage and use.

All containers storing such materials should be labeled with the contents, concentration (if applicable), date of preparation, expiry date, analyst identification and storage conditions. In the case of media, a full documented history or batch record of the process needs to be available. This should include batch of media used, water type, analyst responsible, records of weights, autoclave cycles records, pH adjustments

(including pH meter used), growth promotion (if applicable) and a specific batch number. It is expected that the sterilizing process for any media or reagent will be fully validated. If the media has been externally purchased, certification relating to these parameters must be available.

21.4.5 Reference standards

Microbiological reference standards include antibiotic standards, endotoxin standards, biological indicators and microbial cultures. All of these standards need to be controlled in terms of receipt, storage, preparation and use. Such standards are normally accompanied by a certificate of analysis, and such documentation must be reviewed and be made available. As an example, with endotoxin standards, the certificate of analysis defines the potency of the endotoxin, and thus, the volume required for resonstitution.

21.4.6 Control of microbial cultures

Microorganisms are amongst the most common standards used in the microbiology laboratory. The control and maintenance of stock cultures is critical. Cultures should be controlled from receipt through storage and use, to safeguard the purity and identity of the cultures [7].

During an audit, the preparation, handling and storage of cultures will come under scrutiny. This relates to concerns about misidentification and the potential of viability loss through incorrect storage. For long-term storage there should be no more than five transfers (passages) from the original culture. This is necessary to avoid phenotypic variations.

21.4.7 Documentation and electronic systems

The actual control and information for sample handling may follow a paper based or electronic (laboratory information management system—LIMS) system. If it is an electronic system, it should ensure that where appropriate, any requirements for system validation are met [8]. The auditor will focus on password access and the audit trail.

Log books, equipment files and laboratory notebooks will be subject to inspection. A related, and important area of documentation, is training files. These are invariably called upon during an audit and here each member of the microbiology laboratory must be able to demonstrate that they are trained and assessed in the tasks that they regularly undertake.

21.4.8 Laboratory equipment

The quality of microbiological test data is often dependent upon the performance of instrumentation (for example, an incubator or an air-sampler). It is expected that an inventory of all equipment be available, describing instrument type, serial number,

date of introduction into the laboratory, calibration and validation processes, and a preventative maintenance scheme.

Within the laboratory it is expected that the status of the instrument is verified, for example by labeling whether it is in maintenance or within calibration. A log book for each piece of equipment should be in place to describe what samples have been tested on or with the equipment, what maintenance and so on has been performed. This is helpful in investigations following instrument or sample failure. Auditors will often request calibration certificates, and it is important that these have been fully reviewed and approved.

An example of an important item of equipment is the laboratory autoclave. Autoclave load patterns should be established, assigned to cycles, and tested. Tests should include heat penetration studies and biological challenge tests.

A common audit finding is for equipment service and calibration reports to state that the equipment was adjusted or was actually out of calibration prior to the service and calibration activity without any follow up being recorded.

Different types of equipment will require different levels of validation and calibration, and the criticality of the instrument will determine this in conjunction with a review of the URS. It is essential that items such as water baths, incubators and refrigerators undergo temperature mapping and that during qualification and routine operation thermometers or temperature probes are traceable to national standards.

21.4.9 Cleaning and decontamination

It is important that the results from the microbiology laboratory are representative of the samples being tested and are not the result of cross-contamination. One way to avoid this is through the cleaning and disinfection of premises and equipment.

In addition, if the laboratory has a media preparation area, this must be well maintained. Media preparation requires the use of mixing containers, glassware, balance weighing boats, spatulas, etc. Written, validated procedures should be available for the cleaning and storage of such components.

21.4.10 Specific tests

An auditor will have specific questions to ask about certain laboratory tests. The purpose of this section of the chapter is not to provide an overview of every test, but instead to draw on some illustrative examples.

21.4.11 Microbial limits testing

Microbial limits testing was addressed in Chapter 7. In relation to audits, an auditor may wish to review:

- Growth promotion and suitability using <100 CFU of each individual organism as an inocula level;
- Requirement for comparison to the previous batch of media;

- Addition of 'nutritive' and 'selective' that is the need to demonstrate that media not only recovers the 'target' organism but also inhibits other organisms;
- Enrichment schemes, for example, for *Escherichia coli* and *Salmonella* the test uses soybean-casein media instead of lactose broth;
- Are the test organisms incubated at the correct temperature?

21.4.12 Preservative efficacy test and antibiotic assays

Where preservatives are present in pharmaceutical preparations, the validation of neutralization is important for routine testing. During product development and stability programmes, there could be a requirement to test the effectiveness of the preservative system.

Antibiotic assays should be conducted according to written procedures. Specific requirements that would be reviewed during an audit include media preparation, temperature control (and hence incubator qualification and monitoring, etc.), control of reference standards and assay procedures, for example, plate design (such as Latin square), concentration and volumes of material used. A thorough understanding of the calculations involved in determining potency would be required. It is insufficient for the analyst to simply put the data into a computer programme and accept the result without knowing the background to the evaluation process.

21.4.13 Sterility testing

In an audit, the auditor would look closely at the sterility test validation process. The facility in which the test is performed will come under scrutiny since it is expected to be of a similar quality to that in which the product was manufactured. Therefore, people and material flows would be as defined for the manufacture of sterile products, and the test would be performed under unidirectional conditions (within cleanrooms) or in isolators. Auditors will assess the techniques for transferring samples, media and test equipment into the test environment. Auditors will also review environmental monitoring results, sterility test failure results and the results of test controls, each of which partly informs about the status of the test environment.

21.4.14 Microbial identification

Procedures should be in place for microbial identification methods. It is important that the laboratory can demonstrate that the staff conducting the identifications have a suitable level of knowledge and experience. An auditor will check that appropriate controls are being run with each identification test session.

21.5 Conclusion

As this book has demonstrated, the scope of works undertaken in a typical microbiology laboratory embraces more areas than those described above. The examples are illustrative and are designed to provide some indication of what an audit may cover.

Quality audits serve an important function within pharmaceuticals and healthcare, not least for ensuring that appropriate standards are maintained. The microbiology laboratory plays an important role within the organization, not least for making decisions about the safety of medicinal products. It is therefore important that the highest standards are maintained, and the audit process can assist in helping to meet this requirement.

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