Laboratory management and design

4

4.1 Introduction

To produce results from microbiological analysis of good quality and to carry out such analysis in a safe and controlled way, a dedicated laboratory space is required (the activity of pharmaceutical microbiology should not be shared with other quality control activities such as analytical chemistry). The object of the quality control laboratory is to assess results from the manufacturing process and process environment to ensure that the results produced are free from test errors. To do so requires maintained equipment, ensuring that environmental controls are met, maintaining equipment, and having appropriately trained staff [1]. Furthermore, in relation to good manufacturing practice (GMP), compliance specifically all pharmaceutical quality control laboratories must be run in a compliant manner [2]. A specific area of GMP is dedicated to laboratories (in some GMP systems this is referred to as "good control laboratory practice"; this should not be confused with "good laboratory practice," which refers to animal testing facilities).

This chapter considers some of the important aspects of the design of pharmaceutical microbiology laboratories. The chapter additionally considers the key aspects of the laboratory management function. In doing so, the chapter only provides an overview of the subject, with an emphasis upon control and safety.

4.2 Pharmaceutical microbiology laboratories

Within the pharmaceutical microbiology laboratory, a range of tests are undertaken. These relate to many of the areas discussed throughout the book and invariably include bioburden testing of in-process samples and raw materials; the incubation and reading of environmental monitoring samples; water analysis; endotoxin testing; end product sterility testing; and so forth [3].

The types of microbiological tests, whether the laboratory is dedicated to sterile or to non-sterile activities, can be grouped into:

- *Quantitative examinations*: these measure the quantity of microorganisms present in the sample, and measurements need to be accurate and precise. The measurement produces a numeric value, expressed in a particular unit of measurement. For example, the number of colony forming units obtained from a bioburden sample;
- *Qualitative examinations*: tests that measure the presence or absence of microorganisms (as with the sterility test), or evaluate cellular characteristics such as morphology through microscopic examination. The results are not expressed in numerical terms, but rather in qualitative terms such as "positive" or "negative"; "reactive" or "nonreactive"; "normal" or "abnormal"; and "growth" or "no growth";

Pharmaceutical Microbiology. http://dx.doi.org/10.1016/B978-0-08-100022-9.00004-9

- *Semiquantitative examinations*: are tests that are expressed as an estimate of how much of the measured substance is present. An example here would be the gel-clot form of the limulus amebocyte lysate test.

With each of these types of tests, the laboratory results must be as accurate as possible. To support this, all aspects of the laboratory operations must be reliable and reporting needs to be timely in order for the results to be useful, especially in the event of an out-of-limits result being recorded.

4.3 Laboratory management

The manager of the microbiology laboratory should be someone of experience and qualified in microbiology. The role, depending upon the size of the institution, does not necessarily need to be the same as that of the site microbiologist.

The management function of the laboratory must be responsible for:

- establishing the policies and procedures within the quality system (including suitable standard operating procedures, SOPs);
- ensuring all policies, processes, procedures, and instructions are documented;
- making sure that all personnel understand documents, instructions, and their duties and responsibilities. This requires an efficient training and assessment system;
- providing personnel with the appropriate authority and resources to carry out their duties. This will include biological scientists and microbiologists at graduate level.

To enable these duties to be fulfilled, there needs to be a focus on time management, especially in relation to managing the time of the laboratory staff. Building a hierarchy helps the manager to deal with the workload. Supervisory staff should report to the laboratory manager, and senior scientists should support and train junior scientists.

A second area of importance is with developing the laboratory workflow. A workflow can apply to one or more tests. The sum of operations that are required for a test is called the path of workflow. The path of workflow begins with the sample and ends in reporting and results interpretation. In order to have a functioning quality management system, the structure and management of the laboratory must be organized so that quality policies can be established and implemented.

Arguably the most important laboratory resource is competent, motivated staff. Invariably success or failure depends on the knowledge and skills of the people in the laboratory, and their commitment and motivation to perform tasks as described in the job description (job descriptions should be competency based and reflect any skills needed).

4.3.1 Training

To achieve the necessary level of competence with laboratory staff, a robust and efficient training scheme is required. Training is a process to provide and develop knowledge, skills, and behaviors to meet requirements. In this context, training is linked to the job description and competency assessment and addresses identified gaps in specific tasks to be performed by the employee [4].

On-going training can be assisted through proficiency testing. It is the most commonly employed type of quality assessment, and it can be applied to many laboratory methods. In a typical proficiency test programme, challenge samples are provided at regular intervals (such as two or four times per year). For example, analysts testing samples spiked with known levels of endotoxin and attempt to verify the level, or, alternatively, identifying a cocktail of different types of microorganisms using selective agars and identification methods.

4.3.2 Quality

Laboratory management should have a focus on quality, and this will structured by a quality management system. A quality management system can be defined as the coordinated activities required to direct and to control an organization with regard to quality. This definition is used by the International Organization for Standardization (ISO) [5]. Quality management systems are also a requirement of GMP.

4.3.3 Test methods

Sampling and testing are key features of the test laboratory, and they should be described in SOPs; with SOPs in place for each test. SOPs contain step-by-step written instructions for each procedure performed in the laboratory. These instructions are essential to ensure that all procedures are performed consistently by everyone in the laboratory. An effective SOP should be:

- detailed, clear, and concise, so that staff not normally performing the procedure will be able to do so by following the SOP. All necessary details (e.g., incubation temperature requirements and precise timing instructions) should be included;
- easily understood by new personnel or students in training;
- reviewed and approved by the laboratory management;
- up to date and appropriate.

Sample management is a key part of process control, and thus, it stands as one of the essentials of a quality management system [6]. An important area of management extends to sample control. Each sample should be clearly labeled. SOPs should be extended to cover:

- a description of what samples should be stored;
- the expiry time (with many samples for microbiological testing this can only be for a few hours, such as water samples);
- the location;
- conditions for storage, such as temperature requirements;
- the system for storage organization (one method is to store samples by day of receipt or accession number);
- frequently, samples are collected outside the laboratory and must be transported for subsequent processing and testing, and thus procedures should be extended to cover this.

With test methods, arguably the most important test aspects in relation to pharmaceutical microbiology are microorganisms and culture media. If these are not

controlled in a way to ensure quality, then this undermines the performance of the laboratory. Microbiology requires use of live control organisms to verify that stains, reagents and media are working correctly (this verification requires predictable reactions with microorganisms). These cultures must be carefully maintained in the form of stock and working cultures.

In relation, the quality of media used in the microbiology laboratory must be assessed as suitable for optimal and reliable results. This is in relation to both recovery of certain species and enumeration (media testing is covered elsewhere in this book).

4.3.3.1 Safety

The management role within the laboratory should not simply be focused on test compliance and results reporting. The use of chemicals and other potentially hazardous compounds separates laboratories from other types of building spaces. Protecting the health and safety of laboratory and building occupants must also be a primary concern [7].

A laboratory safety program is important in order to protect the lives of employees and visitors, to protect laboratory equipment and facilities, and to protect the environment. Hence, laboratories must be designed to maintain the health and well-being of occupants. Potentially hazardous substances used in different laboratories include chemicals, radioactive materials, and infectious biological agents [8].

The laboratory manager must ensure that there is an adequate supply of appropriate equipment, such as:

- personal protective equipment (safety glasses, laboratory coat, and gloves);
- fire extinguishers and fire blankets;
- appropriate storage and cabinets for flammable and toxic chemicals;
- eye washers and emergency shower;
- waste disposal supplies and equipment;
- first aid equipment.

Needles, broken glass, and other sharps need to be handled and disposed of appropriately to prevent risks of infection to laboratory and housekeeping staff.

To prevent or reduce incidents caused by exposure to toxic chemicals, all chemicals, including solutions and chemicals transferred from their original containers, should be labeled with their common names, concentrations, and hazards. It is crucial that chemicals are stored properly. Corrosive, toxic, and highly reactive chemicals must be stored in a well-ventilated area, and store chemicals that can ignite at room temperature must be contained in a flammables cabinet.

Laboratory-acquired infections can occur in microbiology laboratories. Aerosols are the main sources of contamination. Such microorganisms should be handled within microbiological safety cabinets (appropriate to the biohazard class of the microorganism).

A related area of infection control is with waste disposal. All waste from the laboratory must be securely bagged. Waste should be either decontaminated on site or removed by a specialist company for incineration. With biohazard 3 and 4 waste, this should always be decontaminated on site.

The laboratory manager should conduct a risk assessment with regard to the activities to be conducted within the facility. All aspects of the work (such as the use of biological agents, ionizing radiation, equipment, or harmful chemicals) must be considered for the assessment [9]. Different countries often have set procedures for conducting risk assessments, many of which are legally binding.

4.3.3.2 Laboratory information management system

An important tool for the laboratory management is an electronic data capture and sample scheduling system. A Laboratory Information Management System (LIMS) is a software-based laboratory and information management system that offers a set of features that support a laboratory's operations. The features include workflow and data tracking support, flexible architecture, and smart data exchange interfaces [10].

LIMS allows for [11]:

- the reception and log in of a sample and its associated data;
- the assignment, scheduling, and tracking of the sample and the associated analytical workload;
- the processing and quality control associated with the sample and the utilized equipment and inventory;
- the storage of data associated with the sample analysis;
- the inspection, approval, and compilation of the sample data for reporting and further analysis.

LIMS has largely replaced paper-based documentation systems.

4.3.4 Lean labs

The "lean" concept has been applied to manufacturing plants for several decades. In recent years, the idea has been applied to laboratories [11]. This is to achieve so-termed "lean labs." With the lean laboratory approach, the adoption of a generic model is unlikely to work due to the differences between laboratories (in terms of staff numbers, types of samples, working practices, types of equipment, and so on). However, the careful adaptation of lean-manufacturing techniques can deliver benefits in terms of productivity, faster testing, and it provides a structured approach to review the necessity of the samples that are processed.

Factors that can affect the performance of the laboratory include:

- *Variable work load*: many laboratories experience variations to their workload, characterized by peaks and troughs. This can lead to times of low productivity during periods when few samples are passing through the laboratory and a failure to meet sample release targets when a high number of samples are passed through the laboratory;
- *Work in progress*: this can occur when too many samples are in a state of "work in progress." Here the laboratory may not release results in a timely or efficient manner. A scenario when this can occur where laboratory technicians efficiently test samples, but they are slow in reading or reporting them.

A related situation is where there is an imbalance with trained staff. In this second scenario, a larger number of technicians may be trained with the initial handling of

samples (such as preincubation steps), but a fewer number are able to complete the tests, leading to hold-ups occurring. In relation, sample throughput can be constructed in a way so that each sample is of equal priority, which removes the need for the inefficient fast tracking of samples;

- *Long and variable lead times*: this situation can occur when samples are grouped and where a test is only run when there is a preset number of samples. While this approach can save costs, if it is maintained irrespective of batch due dates, it can lead to time delays occurring;
- Fast-track systems: this describes urgent samples that can be "fast-tracked" through at the expense of other samples. If the proportion of fast-track samples increases over time, then the situation can become unmanageable;
- *Training gaps*: training gaps refers to situations when there are fewer staff available to engage in testing the variety of different samples that are presented to the laboratory. To avoid this, greater efficiencies can be harnessed through multiskilling the laboratory team.

The lean laboratory approach can address these factors by reviewing the laboratory capacity in order to level out workflow and to harness resources better, orientating resources toward peak times. To add to this, the lean laboratory approach can direct the laboratory manager to conduct a training needs analysis in order to smooth out hold-ups and prevent samples being held as "works in progress." Other aspects include examining how samples are batched together for testing and evaluating if this optimal.

These identified factors can be developed into milestones, which include:

(i) reducing lead times;
(ii) introducing right-first-time concepts to reduce laboratory errors;
(iii) improving approval target times, to address work-in-progress;
(iv) increasing technician productivity, such as number of samples processed per work session.

Another area where the lean laboratory concept can be applicable is with helping to structure a review of the types of samples going through the laboratory.

4.4 Laboratory design

The laboratory work space and facilities must be designed so that the workload can be performed without compromising the quality of work and the safety of the microbiology staff, other laboratory personnel, and visitors.

When developing a laboratory and preparing the layout, it is important to recognize the required work capacity of the laboratory, the number of staff engaged in testing, the services (electricity, water, gas) required, and the mechanisms to control inadvertent release of microorganisms to the environment as well as cross-contaminations. Sufficient space should be provided for all activities to avoid mix-ups. Suitable space should be allocated for sample receipt and processing, reference organisms, media (if necessary, with cooling), testing, and records [12].

Furthermore, the microbiology laboratory is very operator dependent, and for this reason, the design tends to be variable depending upon the array of tasks undertaken. There are, however, areas of commonality and examples of best practice. These areas are considered in Figure 4.1.

Figure 4.1 A typical microbiology laboratory.
Photograph: Tim Sandle.

4.4.1 General design

In general terms, laboratories must be fitted with large areas of bench space and storage areas. Benches must be impervious to water and solvents and must be easy to clean. All joints must be sealed, and the frame itself must be rigid and capable of supporting equipment such as safety cabinets and centrifuges. The benches must be designed to allow comfortable working. To render surfaces free of potentially infectious organisms, all surfaces will need periodic decontamination by disinfectants and, therefore, must be resistant to any such materials.

It is also important that chemically resistant vinyl flooring is used. With finishes, these must be designed and installed with the sealability of the laboratory remaining the primary consideration. There are a number of specialist materials and techniques available on the market for walls and ceilings. These include:

- vinyl cladding;
- polyvinyl chloride sheeting;
- steel panels (of the type used in the nuclear industry);
- polymer paints.

Adequate and accurate safety signage must be provided. Details of emergency contact arrangements must also be clearly displayed.

Provision must be made for sufficient laboratory coat hooks both within the lobby and the laboratory itself. Adequate storage space for clean laboratory coats must be provided within the lobby and laboratory. With microbiology laboratories, laboratory coats should not be worn outside of the department. Gloves should be worn in all instances and should be available to laboratory staff on a routine basis.

4.4.2 Sample collection and testing areas

With sample collection areas, ideally both the reception and the sample collection room are located at the entrance. This can save time and energy. With sample processing areas, this is where samples are allocated for different examinations and dispersed to the appropriate sections of the laboratory for analysis. If possible, the sample processing area should be separated from, but nearby, the testing areas.

With testing areas, ideally there will be separate rooms for the processing of environmental monitoring samples from bioburden samples, in order to avoid cross-contamination. Even where tests are carried out within the same area, measures must be taken to prevent cross-contamination of samples. Dedicated facilities should be available for sterility testing, endotoxin testing, and conducting microbial identifications.

4.4.3 Equipment

There is a variety of different types of equipment that will be required for the microbiology laboratory. These include incubators, refrigerators, microscopes, and autoclaves; such equipment must be maintained and monitored carefully. Ideally, electronic systems will measure temperature-controlled devices and alarm if temperature fluctuations outside of set parameters occur.

Considerable thought and planning should go into equipment management. The following elements should be considered:

- Selection and purchasing: when obtaining new equipment, what criteria should be used to select equipment? For example, should equipment be purchased or would it be better to lease?
- Installation: with new equipment, consider what are the installation requirements and who will install the new instrument?
- Calibration and performance evaluation: what is needed to calibrate the equipment and validate that it is operating correctly? How will these procedures be conducted for both old and new instruments?
- Maintenance: what maintenance schedule is recommended by the manufacturer? Will the laboratory need additional preventive maintenance procedures? Are current maintenance procedures being conducted properly?
- Troubleshooting: is there a clear procedure for troubleshooting for each instrument?
- Service and repair: what is the cost? Can the laboratory obtain the necessary service and repair in its geographical area?
- Retiring and disposing of equipment: what must be done to dispose of old equipment when it needs to be replaced?
- Preventive maintenance requirements. This includes measures such as systematic and routine cleaning, and adjustment and replacement of equipment parts at scheduled intervals;
- Alarm systems for equipment must be in place. To prevent the loss of samples in the event of a freezer or fridge failure.

Prior to testing samples, it is important to evaluate the performance of new equipment to ensure it is working correctly with respect to accuracy and precision. New items of equipment should be qualified. This requires similar steps, as would be applied to production equipment, to be followed: installation qualification, operational

qualification, and performance qualification. A separate, but related, approach will be required for software validation.

With method validation, if the equipment or associated techniques are new, then sample validation processes will need to be considered (in relation to compendial methods, this decision will depend upon the regulatory authority). Validation can be carried out by running samples in parallel using both old and new equipment and methods for a period of time to determine that the expected results can be obtained.

One common item of equipment found in the microbiology laboratory is the autoclave. For successful sterilization to take place, a cycle must be completed at high temperature (100–150 °C) and elevated pressure (1–5 bar) in the presence of moisture, where all of the dry air has been displaced/removed, for a set period of time [13].

4.4.4 Utilities and services

The proper supply of services, such as electrical connections, gases, hot water, demineralized or distilled water, compressed air, vacuum, telephone and data networks, fire protection systems, smoke detection system and alarms, emergency showers, sprinklers, and eye-wash stations, are essential for efficient running of a laboratory.

With water, both hot and cold water pressures must be controlled so that the splashing of the users is limited. Separate wash hand basins must be available. Ideally elbow- or foot-operated systems that do not require hand touching should be used. Dispensers for soap (preferably hands free) and disposable paper towels should be permanently installed immediately adjacent to the basin(s). Due to the air disruption, and levels of contamination, hot air driers should be avoided. In addition to sinks for hand washing and sample disposal, high purity water may also be required.

For incubators and other equipments, the supply of gas (such as carbon dioxide) should be located external to the room and fed through pipework. These penetrations must be fully sealed. The need for gas monitors must be considered. Alarms from these must be audible inside and outside the laboratory.

Consideration should also be given to appropriate levels of lighting. The laboratory should provide suitable illumination; here windows are as important as fluorescent lighting. This is to allow access to natural light and for safety so that those outside can view activities inside. Another factor is sound. In providing a comfortable working environment, noise output from all equipment must be considered and adequately controlled.

4.4.5 Air supply

Three drivers determine the required volume of supply air in a laboratory: temperature, exhaust, and ventilation. Air quality control is needed for the performance of several tests; for operator comfort; and for ensuring that energy usage of efficient. With microbiological tests, some tests require set temperature and humidity ranges. For example, endotoxin testing devices can be affected by high temperatures (above 25 °C).

Consideration should be given to operator comfort. Comfort primarily is concerned with maintaining appropriate temperatures and air velocities. Worker productivity will

be compromised if the space is too warm or too cool. These factors must be considered in relation to design of the air supply. Thermal comfort is of particular importance and must be carefully considered. The over-riding consideration when designing such a system must remain on simplicity.

Control of the air supply should take into account energy efficiency. Conditioning, supplying, and exhausting the large volumes of air used in laboratories consumes sizeable quantities of energy. Reducing these energy costs often forms part of the laboratory management function.

4.4.6 Clean air devices and containment

Containment laboratories must be designed and built to prevent or control the exposure of laboratory workers, other persons, and the environment to the biological agent in use. With biological agents, microorganisms are commonly placed into biohazard groups. The terms applied to the groups vary according to different regions of the world; however, they generally conform to four hazard groups (1 being lowest risk, 4 being highest) on the basis of their infectivity and the consequences of such infection [14].

For microbiology laboratories, the levels of containment usually required for work with such agents are determined by their categorization (e.g., containment Level 3 is required for Hazard Group 3 pathogens), and these reflect the increasing levels of health risk to people involved in (or who could be affected by) such work.

In order to minimize risk, most laboratories will have two physical layers of containment. The primary barrier (safety equipment), which will contain the hazard at source, and the secondary barrier (the laboratory itself), the design of which is essential in protecting both the worker and people outside the laboratory. All air leaving the containment room must pass through a HEPA (high efficiency particulate air) filter. As a further measure, laboratories are maintained at a lower pressure than surrounding areas (negative pressure), in order to prevent contaminants from spreading through a building. In constant volume laboratories, the supply and exhaust airflows are balanced to always maintain a given airflow.

Work involving hazardous microorganisms should be undertaken within a microbiological safety cabinet. Such cabinets are designed to protect the operator from the microorganism and to prevent cross-contamination of the microorganism itself. Care must be taken in positioning equipment that might generate air currents (such as fans and heaters). The safety cabinets should be installed in suitable sites in the laboratory.

Fume hoods are safety devices that are used to contain chemicals with long-term exposure hazards. Fume hoods are not appropriate for protection from substances causing significant health consequences with only isolated, short-term exposures.

4.5 Conclusion

This chapter has examined the microbiology laboratory and, in doing so, has considered laboratory management, which is based around the planning of personnel and resources, and the appropriate design of a microbiology laboratory. Design needs to

be based on the objectives of safety and efficiency. Most importantly, microbiology laboratories should be designed to suit the operations to be carried out within them (as a part of the quality-by-design philosophy, in which quality is built in at the outset and not added to afterward).

Consideration should also be given to the laboratory space. Future expansion of activities, including increases in workload and staff. The design should include provision for a minimum of 25% of expansion. The structure should be flexible to allow room functional changes and allocation of new activities.

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