Introduction to pharmaceutical microbiology

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1.1 Introduction

Microbiology is a biological science involved with the study of microscopic organisms. Microbiology is made up of several sub-disciplines, including: bacteriology (the study of bacteria), mycology (the study of fungi), phycology (the study of algae), parasitology (the study of parasites), and virology (the study of viruses, and how they function inside cells) [1]. These broad areas encompass a number of specific fields. These fields include: immunology (the study of the immune system and how it works to protect us from harmful organisms and harmful substances produced by them); pathogenic microbiology (the study of disease-causing microorganisms and the disease process (epidemiology and etiology)); microbial genetics (which is linked to molecular biology); food microbiology (studying the effects of food spoilage); and so on [2].

The microbiological discipline of relevance here is pharmaceutical microbiology, an applied branch of microbiology (once considered as an off-shoot of industrial microbiology but now a distinct field). Pharmaceutical microbiology is concerned with the study of microorganisms associated with the manufacture of pharmaceuticals. This is with either using microorganisms to help to produce pharmaceuticals or with controlling the numbers in a process environment. This latter concern is about ensuring that the finished product is either sterile or free from those specific strains that are regarded as objectionable. This extends through the manufacturing process, encompassing starting materials, and water. Pharmaceutical microbiologists are additionally interested in toxins (microbial by-products like endotoxins and pyrogens), particularly with ensuring that these and other "vestiges" of microorganisms (which may elicit adverse patient responses) are absent from products.

Microbiological contamination becomes a problem when it results in unwanted effects occurring in pharmaceutical preparations. In drawing from risk assessment terminology, pharmaceutical microbiology centers on understanding the likelihood of product contamination arising; understanding the severity of such contamination; considering ways to minimize contamination; and, where contamination cannot be satisfactorily mitigated, using established and developing new methods to detect contamination.

To understand the severity, it is necessary to understand the type of product, its intended use, and the nature and numbers of contaminants. Microbial contamination of sterile injectable products (parenterals) presents the greatest risk, for this may lead to death of the patient, whereas with other products, aromas, off-flavors, or discolorations, caused by microorganisms, may have fewer adverse effects. Therefore, with respect to sterile products, the main concern is with any potential microbial contamination. With

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nonsterile products (such as inhalations, tablets, oral liquids, creams, and ointments), a level of microbial contamination may be tolerated, with a greater concern centered on the presence or absence of "objectionable microorganisms." The types of microorganisms of concern depend upon the type of product and route of administration [3].

The foundation of pharmaceutical microbiology is use of culture media: these are nutrients and growth factors designed to cultivate and grow bacteria and fungi. This foundational basis is being partially eroded through the increased use of rapid and alternative microbiological methods, although even here a substantial number of these methods remain growth based. The over-riding technique that the microbiologist must apply is an "aseptic technique" (the prevention of contamination during the manipulation of samples and cultures). The growth of microorganisms and the maintenance of aseptic technique require trained and skilled microbiologists [4].

This chapter, as a way of a short introduction to the various texts in this book, outlines the essentials of pharmaceutical microbiology, many of which are discussed in detail throughout this book.

1.2 Overview of pharmaceutical microbiology

Pharmaceutical microbiology is the application of microbiology to pharmaceutical and healthcare environments. The scope of pharmaceutical microbiology is wide ranging. However, its over-riding function is the safe manufacture of pharmaceutical and healthcare preparations and medical devices. This involves risk assessment (both proactive and reactive), together with testing materials and monitoring environments and utilities.

Some of the essential tests are described in the three main international pharmacopoeias: United States, European, and Japanese. These include:

- sterility test;
- bacterial endotoxin test;
- microbial enumeration methods, such as the microbial limits test;
- tests for specified microorganisms;
- antimicrobial susceptibility testing;
- methods and limits for testing pharmaceutical grade water;
- disinfectant efficacy;
- pyrogen and abnormal toxicity tests;
- environmental monitoring;
- biological indicators.

Many of the tests associated with the above list are the subject of chapters in this book. Beyond these, pharmaceutical microbiology continues to evolve, and the book considers contemporary developments within the field.

It would be a mistake to think of pharmaceutical microbiology as confined to a range of laboratory tests. The concept of "testing to compliance" is outdated. To address contamination risks, pharmaceutical microbiology places an emphasis upon contamination control. For this reason, pharmaceutical microbiologists are involved in a number of aspects of the production process, utility supply, and cleanroom

environments. This generally involves testing and the assessment of data; conducting risk assessments, either proactively or in response to a problem; and helping to design systems as part of a contamination control strategy. These twin areas of testing and control are intermixed throughout this book.

1.3 Microbiological test methods

With testing, microbiological test methods can typically be divided between:

- Qualitative methods—where the object is to ask "Is there something there?" (such methods are concerned with the presence or absence of all microorganisms or specific species);
- Quantitative methods—this is concerned with the question "How many are there?," and this centers on enumeration methods;
- Identification methods—here the focus is the question "What are they?," and the topic is the characterization and identification of microorganisms.

This section examines the work of the microbiologist in relation to the key test areas that are required to assess the pharmaceutical processing environment (Figure 1.1).

1.3.1 Product-related testing regimes

The microbiologist should be involved in establishing the sampling and testing regime in order to assess the microbiological quality of the pharmaceutical manufacturing process. This involves selecting, sampling, and testing:

- starting materials;
- in-process samples or intermediate product;
- examination of final product formulations;
- testing of the final product.

Figure 1.1 Technician working in a pharmaceutical microbiology laboratory. Photograph: Courtesy of pharmig.

Where tests are described in pharmacopeia (of which the major global texts are the United States, European, and Japanese), then since 2000 there has been a concerted global effort to harmonize compendia [5].

1.3.2 Starting materials

The majority of starting materials (raw materials) will have pharmacopoeial monographs that will indicate the type of microbiological testing required. Depending upon the nature of the material, the intended process step, and final product requirements, additional testing may need to be considered. With a nonsterile product, for example, a presence–absence test for an objectionable microorganism not description in a pharmacopoeial monograph may be required (as discussed in Chapter 8).

Some types of starting materials may not have a supporting pharmacopoeial monograph. In such circumstances, the microbiologist will need to decide the appropriate testing regime.

The testing required on starting materials is normally divided into the following microbial limits tests:

- microbial enumeration (which is divided into tests for the total microbial count and the total yeast and mould count);
- presence–absence of specific indicator microorganisms (which may be considered objectionable to the product or process).

These two sets of tests are outlined in the United States, European and Japanese pharmacopeia (see: USP <61>/Ph. Eur. 2.6.12 "Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests" and USP <62>/Ph. Eur. 2.6.13 "Microbiological Examination of Non-Sterile Products: Tests for Specified Microorganisms").

With specified microorganisms, these are designed as indicators of potential sources of contamination. Test organisms include:

- bile-tolerant Gram-negative bacteria;
- *Salmonella*;
- *Escherichia coli*;
- *Pseudomonas aeruginosa*;
- *Staphylococcus aureus*;
- *Candida albicans*;
- Clostridia.

Not every test organism is applicable to each material. Often a pharmacopoeial monograph for a material will specify which organisms need to be examined for. Additionally, some materials required examination of endotoxin:

- Bacterial endotoxin testing.

The primary test method is the *Limulus* amebocyte lysate (LAL) test. Endotoxin testing is outlined in USP <85>/Ph. Eur. 2.6.14.

All samples should be qualified to demonstrate the ability to recover known challenges of recommended compendial organisms using the methods required (note: with the compendial methods, these methods are not required to be "validated"; however,

the suitability of a given method for a particular sample must be demonstrated). Where required, representative microorganisms from the manufacturing environment can be included as a part of the assessment. With the qualification, consideration should also be given to the need for neutralization agents in the media to remove any inherent antimicrobial properties in the starting materials.

With the microbiological testing of starting materials, there may be a case for reduced testing (often in the form of skip-lot testing). This is often assessed on the basis of past test results, and the information provided by the microbiologist will be of importance in making such a case.

1.3.3 In-process samples/intermediate product

As a product is being manufactured, it is typical for in-process samples, at representative stages or points in the process where there is considered to be a risk, to be taken and submitted to the microbiology laboratory for bioburden testing. Bioburden, as Chapter 7 expands upon, is a general descriptive term for the number of bacteria living on a surface or in a material. Bioburden is normally assessed using the total viable count (TVC) method, where a portion of the sample is added to agar or agar in a receptacle is used to assess the surface of the sample. TVC provides a quantitative idea about the presence and numbers of microorganisms in or on a sample. The result obtained represents the number of colony-forming units (CFUs) per gram (or per milliliter) rather than the actual number of microorganisms present (Chapter 7 discusses this subtle, yet important, difference). Rapid microbiological methods can be used as alternatives to the pharmacopeia methods, with justification and regulatory approval [6].

For some specific process steps, such as water rinses, endotoxin testing should also be considered. In addition to samples of intermediate product, other samples can provide important information as to the risk of contamination. Such samples include granulation solutions, coating solutions, suspensions for spray drying, buffers, water rinses, and so on.

A risk assessment should be conducted for all samples submitted (to ascertain what a bioburden above a pre-defined action level means, should it occur), and this should be appropriately documented. With alert and action levels, typically there are no published limits for intermediates or in-process samples with the exception of the final bulk prior to final sterilization in aseptic manufacturing.

A further consideration is the validation of sample hold times for the microbiologist will need to establish the appropriate time between the time of sampling and testing. Typically maximum hold times are 24 h, put in place to avoid over-growth of microorganisms. The time between a sample being taken and tested should also be evaluated (during this period, samples are normally held at 2–8 °C).

1.3.4 Final product formulations

For aseptic manufacturing, it is important that the stage prior to final sterilizing filtration—(the sterile bulk) is tested. (The extent of the testing will depend upon whether the bulk is filled within a short space of time of the same site or transported elsewhere.)

As a minimum, a sample should be taken for bioburden testing. The recommended limit is 10 CFU/100 mL (for Europe this is as defined by the Committee for Proprietary Medicinal Products (as set out in CPMP QWP/486/95)) [7]. Depending upon the risk assessment, an endotoxin test is also normally conducted with a limit applicable to the final product.

Sterilizing grade filters require microbiological validation. This normally involves challenging the product with a diminutive microorganism (such as *Brevundimonas diminuta*) of a high population (typically 10^7 organisms per cm^2 of filter surface) and determining if the filter retains the microorganism or whether any of the microorganisms pass through into the filtrate [8]. Microbiologists should play a role in coordinating such studies [9].

For terminally sterilized products, it is typical for the presterilization bioburden to be assessed. This is to determine whether the microbial numbers and species types exceed the population and resistance of the microorganism used to establish the sterilization cycle. Sometimes this assessment is used as a part of parametric release in lieu of an endproduct sterility test (Figure 1.2; [10]).

1.3.5 Finished product

The finished product, for nonsterile and sterile products, must always be subject to microbiological testing. For sterile products, the testing requirements and specifications are typically defined in the pharmacopoeia. This includes the sterility test (where the product must be free from viable microorganisms) and normally an endotoxin or pyrogen test (here the limit will depend on the dose, application and intended patient type and limit calculation following the guidance in the pharmacopoeias). Some organizations will also conduct an abnormal toxicity test, using an animal model.

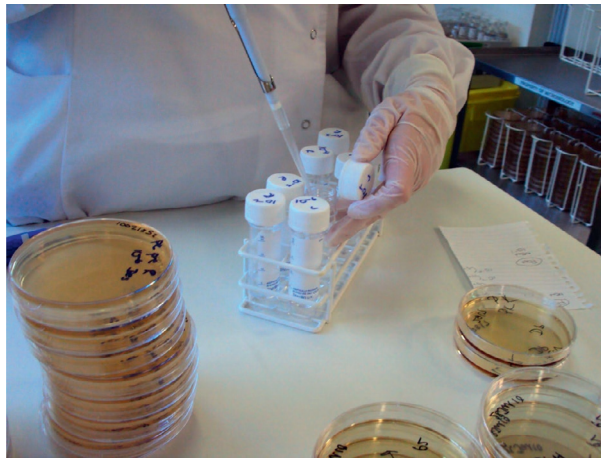

Figure 1.2 Analyst performing bioburden testing.
Photograph: Tim Sandle.

For nonsterile products, the product will typically have a specification based on the maximum permitted microbial count, and there will be a requirement for the product to be free from certain objectionable microorganisms (this is discussed later in Chapter 8). At an early stage of the product development, the microbiologist will need to be involved in establishing the specifications. This will normally be based on the preliminary testing and characterization of the product. At this stage, any requirements for neutralization of media to combat inherent antimicrobial activity of the product should also be established.

1.3.6 Testing of utilities

Pharmaceutical microbiologists are involved with the testing of various utilities that support production processes. This includes compressed gases (which are examined for microbial count and particulates), steam (which is typically examined, as condensate, for bacterial endotoxin), and, most importantly, pharmaceutical grade water. Pharmaceutical grade water includes water-for-injection (WFI) and purified water. In addition, feed water (mains water is examined). Water samples will provide an indication of the microorganisms that are circulating in the water, although they can underestimate the extent of any biofilm communities that might have formed on pipework.

Water systems are examined for:

- total aerobic microbial count;
- bacterial endotoxins;
- specific microorganisms.

With these tests, samples for microbial count are typically tested using an agar especially designed for water systems: Reasoner's 2A (R2A) agar, although other media can be used depending upon the type of water (notably, the European Pharmacopeia specifies R2A although other compendia are less specific with the selection of culture media). The method of choice is the membrane filtration method although plate counts are sometimes performed where a higher bioburden is expected from lower quality types of water. Endotoxin tests are not required for all types of water. Pharmacopoeias require the endotoxin test to be conducted for WFI and for highly purified water only. Some manufacturers also elect to test certain parts for the water system for specific microorganisms such as *E. coli* (an indicator of fecal contamination). This might include the incoming mains water, depending upon what is conducted by the water provider (such as a municipal water company). Other objectionable microorganisms can also be screened for or surveyed through the microbial identification of "out of specification" (OOS) samples.

The method for testing of water and recommended action limits are provided in the applicable pharmacopoeial monographs; however, as with environmental monitoring, it is expected that internally derived alert levels are set based upon the historical performance of the system. The frequency of monitoring depends on the state of the water system (whether it is under qualification or not) and the quality of the results. The microbiologist will need to determine suitable frequencies; here samples of WFI are typically taken each working day with the outlets on a rotational system. To achieve

this, samples are taken, aseptically, at representative points of use. Other water systems are sampled less often.

The trend for a given water system or outlet is, in many ways, of more importance than individual excursions above operating limits. Trend analysis of water systems should be undertaken on a regular basis.

1.3.7 Environmental monitoring

Microbiological environmental monitoring is a key part of the assessment of pharmaceutical manufacturing facilities. Environmental monitoring data indicates if cleanrooms are operating correctly (cleanrooms are the fabric within which pharmaceutical manufacturing takes place). Other information relating to contamination control is derived from an assessment of the heating, ventilation, and air conditioning (HVAC) parameters, which contribute toward making the cleanroom "clean." These parameters include temperature, humidity, pressure, room air changes, and air-flow patterns. The microbiologist must be familiar with these.

Environmental monitoring is divided into viable and nonviable monitoring. Viable monitoring is the examination of microorganisms (bacteria and fungi) located within the manufacturing environment.

The most important element for a microbiologist to establish is the overall monitoring program. This involves the consideration of a number of factors, which include:

- the monitoring methods (to assess air, surface, and personnel contamination);
- culture media (such as general purpose media or fungal specific media) and whether a disinfectant neutralizer is required;
- incubation times and temperatures;
- sampling procedures;
- sample locations within the cleanroom;
- frequency of monitoring;
- room conditions for the sampling (at rest or in operation);
- who undertakes the monitoring (production or quality control (QC)) staff;
- establishing alert and action levels;
- guidance on dealing with out of limits results;
- characterization of the microflora.

These various considerations should be incorporated into a policy and into a plan. From this, local standard operating procedures (SOPs) should be generated. Environmental monitoring programs should adapt to changes to the pharmaceutical manufacturing environment and, therefore, the program should be regularly reviewed.

There are inherent weaknesses with environmental monitoring programs. Environmental monitoring data only provides an indication of the background environment of a cleanroom at the time it as used. A single result may or may not be representative of the longer-term room conditions. Furthermore, the methods are very insensitive, and they cannot be "validated" in the way that an analytical method can be. In addition, the frequency of samples and locations in which the samples are taken may or may not indicate the actual level of contamination risk, and there

is often no direct correlation between number of organisms found and product contamination risk [11].

1.3.8 Other microbiology laboratory tests

There is a range of other tests that pharmaceutical laboratories may be involved in. These are:

- microbial identifications;
- water activity;
- disinfectant efficacy testing;
- antimicrobial susceptibility testing;
- microbial immersion studies;
- cleaning validation studies;
- maintenance of microbiological cultures;
- advising on process and equipment design;
- conducting risk assessments;
- investigation of out of limits results;
- maintenance of laboratory equipment;
- laboratory training.

1.4 The application of pharmaceutical microbiology

In undertaking the activities of pharmaceutical microbiology, there are a number of important points that should be kept in the forefront. These points range from counting methods and aseptic sampling to knowledge of objectionable microorganisms. They are presented here because they frame the assumptions of many of the tests outlined later.

1.4.1 Counting

One of the important tasks required by pharmaceutical microbiologist is the ability to enumerate microorganisms. Counting is required in order to assess the microbial quality of water, in-process bioburden samples, of raw materials, and so on. The method used to count microorganisms depends upon the type of information required, the number of microorganisms present, and the physical nature of the sample. An important distinction is between total cell count (which counts all cells, whether alive or not) and the viable count (which counts those organisms capable of reproducing).

Total cell counts include direct microscopic examination, the measurement of the turbidity of a suspension (using a nephelometer or spectrophotometer), and the determination of the weight of a dry culture (biomass assessment), adenosine triphosphate (ATP) measurements (typically using the enzyme luciferase that produces light on the hydrolysis of ATP) fluorescent staining, or electrical impedance. Viable counting techniques include the spread plate, pour plate (through direct plating or an application like the Miles–Mistra technique), spiral plating, and membrane filtration.

1.4.2 Sampling

An important aspect of the work of pharmaceutical microbiologists is ensuring that the samples taken or submitted to the laboratory have been done so in an aseptic manner and that the containers and storage conditions of the sample have not been adversely affected.

The containers selected must normally be sterile (either disposable plastic or autoclaved glassware), and the containers should not leech out any chemicals that might have antimicrobial properties and thereby give a false-negative result. The sampling technique used, irrespective of the sample type, must ensure that the hygiene of the sample is maintained (aseptic technique). This requires the person taking the sample to have been appropriately trained. The sample must also be transported in a sound manner and stored under appropriate conditions (in-process and water samples are normally required to be placed at 2–8 °C within 1 or 2 h of sampling).

In terms of the numbers of samples taken or the amount collected, the sample should be representative. This means that the sample should be of sufficient volume (such as 200 mL of pharmaceutical grade water) or an appropriate number of samples should be taken in order to produce a representative result (e.g., determining how many samples from a give number of containers of a raw material will give a representative result. There are different statistical tools which can be used for this purpose, the most simple being the square root of the number of containers). A further issue is with the sample being representative. For example, a water sample collected for microbiological analysis should be taken in the way that a production operative would use it; a raw material sample taken from a container should be of the mixed sample, so that it is homogenous; and so on. This is because microorganisms rarely follow normal distribution, and it may sometimes be that more than one sample is required for a final result to be closer to the "true" bioburden.

1.4.3 Microorganisms detected from pharmaceutical manufacturing environments

Studying the range, types, and patterns of microorganisms found in cleanrooms can provide essential information for microbiologists and quality personnel in understanding cleanroom environments and for assisting with contamination control. Such studies can prove to be very useful for microbiologists in benchmarking the types and frequency of incidence of the more common microorganisms likely to occur in cleanrooms. This is an important feature of ensuring good microbiological control [12].

Two aspects of screening microbiota are to note possible resistant strains and objectionable microorganisms. Where repeated occurrences of microorganisms occur in the environment, particularly Gram-positive sporing rods and certain Gram-negative rods, then this may be an indication of an ineffective cleaning and disinfection regime [13]. Microorganisms pose a contamination risk to pharmaceutical processing. It is important that pharmaceutical manufacturers undertake adequate cleaning and disinfection to reduce the risk of microorganisms proliferating. For this, a variety of

disinfection agents may be used depending on the types of microorganisms. Prior to the purchase of new disinfectants, internal validation studies need to be undertaken in order to confirm the effectiveness of the disinfectant using recommended type cultures and "in-house" environmental microorganisms. Microbiologists should be involved with cleaning validation, where an assessment is made of the ability of an automated or manual process to remove microorganisms as well as chemical impurities [14].

The concern with objectionable microorganisms from regulators is primarily aimed at non-sterile products (creams, ointments, tablets, and so on). Many of the species considered to be "objectionable" are described by the US Food and Drug Administration (FDA) [15]. When objectionable microorganisms occur, the advice of Sutton is to conduct a risk assessment.

Risk assessment criteria may include:

(a) Absolute numbers of organisms seen.

High numbers of microorganisms may affect product efficacy and/or physical/chemical stability. An unusually high number of organisms seen in the product may also indicate a problem during the manufacturing process, or an issue with a raw material. The high bacterial counts may also indicate that the microorganisms are thriving in the product.

(b) The type of microorganisms and the characteristics of the microorganism.

The type of microorganism provides information that will indicate its probable origins and the potential risk it may pose to the product or to the environment.

(c) Considering if the microorganism can survive.

This can be based on the following factors:

- pH;
- salt concentrations;
- sugar concentrations;
- available water;
- temperature;
- time.

Survival is generally lower under the following conditions:

- low or high pH;
- high salt concentrations;
- high sugar concentrations;
- low presence of water;
- temperatures above 45 °C (except for thermophilic spores);
- low temperatures below 10 °C (although this may inhibit growth rather than destroy cells);
- freezing.

(d) Product characteristics.

The dosage form of the product is important to consider, particularly whether the material is anhydrous or water based. This can have an effect on the ability of microorganisms to proliferate. Here, whether the product contains sufficient free water to support microbial growth is a key factor.

(e) Potential impact on patients.

Assessing the risk to patients from viable microorganisms or from toxins is the aspect of risk assessment that is the most important consideration.

With both sterile and nonsterile products, objectionable microorganisms pose a concern in relation to [16]:

(a) toxins and other microbial by-products;
(b) diminutive microorganisms that may pose a challenge to sterilizing grade filters;
(c) the microbial bioburden of incoming raw materials (when assessed against the microbial limits test);
(d) as indicator organisms that may signal a concern with a utility (such as fecal coliforms in water);
(e) microorganisms with the potential to affect integrity of container/closure system;
(f) an organism that signals a concern with personnel (such as poor personal hygiene);
(g) an unusual microorganism that signals a change in the established microflora in the environment;
(h) a possible weakness with the microbial identification system (i.e., an organism that is characterized but is considered to be so unlikely to occur within a pharmaceutical environment that a misidentification may have occurred, which is sometimes possible with phenotypic techniques). Identification methods are outlined in Chapter 9;
(i) understanding the types of microorganisms provides an indication of the origin of the contamination.

1.4.4 Contamination control strategy

The tests described, and the awareness of the areas of risk throughout the manufacturing process, should feed into a contamination control strategy. This should be a formal, high-level document to which microbiologists should make a major contribution. With such documents, the foremost consideration should be that pharmaceutical medicines are to be manufactured to be safe and efficacious. The presence of microorganisms in pharmaceutical preparations can have an adverse effect on the effectiveness of the preparation, and it may cause harm to the patient. The risk of the microorganism causing harm depends upon the type of product, the way it is administered, and the health of the patient who is receiving the medicine.

1.4.5 Advances in pharmaceutical microbiology

Recent advances in pharmaceutical microbiology relate to progress made with rapid and alternative microbiological methods; and with advances in the characterization of microorganisms, which have led to a re-interpretation of microbial taxonomy.

Rapid microbiology is a reference to microbiological testing that is evolving beyond traditional methods where microorganism detection requires days or weeks to technologies that can produce a result in a much faster time. Many rapid microbiological method technologies provide more sensitive, accurate, precise, and reproducible test results when compared with conventional, growth-based methods. Furthermore, they may be fully automated, offer increased sample throughput, operate in a continuous data-collecting mode, and provide significantly reduced time-to-result (sometimes in “real-time”).

Rapid microbiological methods and alternative methods are often used as interchangeable terms, although more strictly “alternative methods” refers to techniques that differ to those described in compendia. Many rapid and alternative methods can

also detect microorganisms that are present in a sample (or within an environment) but that cannot be easily cultured. This is because the microorganisms are either stressed or sub-lethally damaged or because they simply cannot grow on standard culture media. Such microorganisms are referred to as "viable but non-culturable" or "active but non-culturable" [17]. Rapid methods are discussed in Chapter 17.

Microbiological understanding of people and how they relate to the surrounding world has advanced considerably following the publication of the key findings from the first wave (2008–2013) of the Human Microbiome Project. These findings not only confirmed that the human body is an intricate system that hosts trillions of microbial cells, across the epithelial surface, and within the mouth and gastrointestinal tract; it also demonstrated that microorganisms play a complex role in human physiology and organ function, influencing digestion, immunity and development [18]. The microbial community also affects the way that different medicines work in the body, leading to possibilities of medicines tailored for different individuals based on the genetic interactions between the individual and their microbial communities.

The Human Microbiome Project has also directed the development of new genotypic and molecular methods (the most prevalent methods use comparative deoxyribonucleic acid (DNA) sequencing of the 16S ribosomal ribonucleic acid (rRNA) gene in bacteria and a region associated with the 26S rRNA gene in fungi). The use of these methods has led to advances with identification and the re-classification of the bacterial and fungal kingdoms [19]. Moreover, metagenomics (the study of genetic material recovered directly from environmental samples) has led to a greater understanding of how microorganisms interact with, and have an influence on, their hosts and the surrounding environment.

1.5 Conclusion

This chapter is an introduction to the more detailed aspects of pharmaceutical microbiology that are discussed throughout the rest of this book. The purpose of the chapter was to provide an overview of some of the specifics of pharmaceutical microbiology. Pharmaceutical microbiology covers a very large area and this chapter can only touch on some of the more common and essential elements. In doing so, the chapter has bridged the laboratory testing side of pharmaceutical microbiology with the contamination control side. These sides are sometimes inelegantly split between "QC" and "quality assessment" microbiology. This is unfortunate, for microbiology should not be artificially separated and instead each organization should have in place a site microbiologist who can keep both parts focused on contamination control.

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