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⟨1117⟩ MICROBIOLOGICAL BEST LABORATORY PRACTICES

Add the following:

Change to read:

INTRODUCTION

Good ▲▲ (USP 1-Aug-2022) practices in a microbiology laboratory consist of activities that depend on several principles: aseptic technique, control of media, control of test strains, operation and control of equipment, diligent recording and evaluation of data, and training of the laboratory staff ▲in related competencies.▲ (USP 1-Aug-2022) Because of the inherent risk of variability in microbiology data, reliability and reproducibility are dependent on the use of accepted methods and adherence to good ▲practices in the laboratory. This chapter does not cover the unique and specific laboratory activities for virology and mycoplasma recovery and detection.▲ (USP 1-Aug-2022)

Change to read:

MEDIA PREPARATION AND QUALITY CONTROL

Media Preparation

Culture media are the basis for most microbiological tests. ▲Culture media may be either prepared in-house or obtained commercially. The term “prepared media” used in this chapter covers both these types of media.▲ (USP 1-Aug-2022) Safeguarding the quality of the media is therefore critical to the success of the microbiology laboratory. Media preparation, proper storage, and quality control testing can ensure a consistent supply of high-quality media.

It is important to choose the correct media or components in making media based on the use of accepted sources or references for formulas. The manufacturer's formula and instructions for preparation routinely accompany dehydrated and ready-made media. Because different media types may have different preparation requirements (e.g., heating, additives, and pH adjustment), it is important to follow these instructions to ensure preparation of acceptable media quality. A certificate of analysis describing expiration dating and recommended storage conditions accompanies ready-made media, as well as the quality control organisms used in growth-promotion ▲testing, inhibitory and indicative property testing, as appropriate, and the results of performance testing with acceptance criteria for that media. For in-house prepared media, similar quality control criteria should be established.▲ (USP 1-Aug-2022)

Water is the universal diluent for microbiological media. *Purified Water* is most often used for media preparation, but in certain cases the use of deionized or distilled water may be appropriate. Water of lesser quality should not be used for microbiological media preparation. The volume of the water used should be recorded.

Consistent preparation of media requires accurate weighing of dehydrated media or media constituents. A calibrated balance with the appropriate weight range for the ingredients should be used (see *Weighing on an Analytical Balance* ⟨1251⟩). Clean weighing containers and tools (such as spatulas) should be used to prevent foreign substances from entering the formulation. The weight of the components should be recorded.

Dehydrated media should be thoroughly dissolved in water before dispensing and sterilization. If heating is necessary to help dissolve the media, care should be taken not to overheat the media because all culture media, to a greater or lesser extent, are heat-sensitive. Equipment used in the preparation of media should be appropriate to allow for controlled heating, constant agitation, and mixing of the media. Darkening of media (Maillard-type reaction or nonenzymatic browning) is a general indication of overheating. When adding required supplements to media, adequate mixing of the medium after adding the supplement should be performed.

Preparation of media in poorly cleaned glassware can allow inhibitory substances to enter the media. Inhibitory substances can come from detergent residue after cleaning glassware or from prior materials used in the glassware. Be sure that the cleaning process removes debris and foreign matter, and that the detergent is thoroughly rinsed out with *Purified Water*. See *Cleaning Glass Apparatus* ⟨1051⟩ for additional guidance.

Sterilization of media should be performed within the parameters provided by the manufacturer or validated by the user. Commercially prepared media should provide documentation of the sterilization method used. Autoclaving by moist heat is the preferred sterilization technique, except in instances when boiling is required in order to avoid deterioration of heat-labile components of the media. Sterilization by filtration may also be appropriate for some formulations.

The effects of the sterilization method and conditions on the media should be validated by sterility and growth-promotion testing of the media. In addition, if sterilized by moist heat, the autoclave cycle should be validated to ensure proper heat distribution for selected loads and volumes. Typically, manufacturers recommend an autoclave cycle of 121° for 15 min using a validated autoclave. These conditions apply to time at temperature of the media. As container size and the load configuration of the autoclave will influence the rate of heating, longer cycles may be required for larger loads.▲▲ (USP 1-Aug-2022) Sterilization time will be dependent on the media volume and autoclave load. Sterilization cycles in which the autoclave is slow to come up ▲or come down▲ (USP 1-Aug-2022) to temperature may result in overheating of the media. Therefore, care must be taken to validate a sterilization cycle, balancing the need for sterile media against the tendency of the media to degrade under excessive heating. ▲Holding▲ (USP 1-Aug-2022) of the media in the autoclave after the liquid ▲or slow exhaust cycle▲ (USP 1-Aug-2022) is completed is not recommended after cooling, as it may damage the media. Improper heating or sterilizing conditions—for commercially prepared or internally prepared media—may result in a difference in color,▲▲ (USP 1-Aug-2022) loss of clarity, altered gel strength, or pH drift from the manufacturer's recommended range, as well as reduced growth-promotion activity and/or selectivity. ▲All sterilization cycle parameters should be documented.

Unless it is specified to confirm the pH of the medium prior to the sterilization process,▲ (USP 1-Aug-2022) the pH of each batch of medium should be confirmed after it has cooled to room temperature (20°–25°) by aseptically withdrawing a sample for testing. Refrigerated purchased media should be allowed to warm up to ambient room temperature if it is to be checked for pH confirmation. A flat pH probe is recommended for agar surfaces, and an immersion probe is recommended for liquids. See *pH* ⟨791⟩ for guidance with pH measurement and instrument calibration. The pH of media should be in a range of ±0.2 of the value indicated by the manufacturer unless a wider range is acceptable by the validated method.

Prepared media should be checked by appropriate inspection of plates and tubes for the following ▲quality and integrity parameters:▲ (USP 1-Aug-2022)

- Cracked containers or lids
- Unequal filling of containers
- Dehydration resulting in cracks or dimpled surfaces on solid media

- Hemolysis
- Excessive darkening or color change
- Crystal formation from possible freezing
- Excessive number of bubbles
- ▲▲ (USP 1-Aug-2022)
- Status of redox indicators (if appropriate)
- Lot number and expiration date ▲▲ (USP 1-Aug-2022)
- Sterility ▲▲ (USP 1-Aug-2022)
- Cleanliness of plates (lid should not stick to dish)

Media Storage

It is prudent to ▲understand▲ (USP 1-Aug-2022) how the manufacturer or supplier transports and stores media before distribution to the end user. Manufacturers of media should use transport and storage conditions that minimize the loss of moisture, control the temperature, prevent microbial contamination, and provide mechanical protection to the prepared media.

Media should be labeled properly with batch or lot numbers, preparation and expiration dates, and media identification. Media should be stored according to the manufacturer's instructions. Media prepared in-house should be stored under validated conditions. Do not store ▲media plates containing▲ (USP 1-Aug-2022) agar at or below 0°, as freezing could damage the gel structure. Protect stored media from exposure to light, excessive temperature, ▲and temperature changes, *as this may cause condensation*. Consideration should be given to storing agar plates in▲ (USP 1-Aug-2022) a sealed package or container to ▲prevent▲ (USP 1-Aug-2022) moisture loss ▲from the plates.▲ (USP 1-Aug-2022)

Remelting of an original container of solid media, ▲if not containing heat-labile components (*1*),▲ (USP 1-Aug-2022) should be performed only once to avoid media whose quality is compromised by overheating or potential contamination. It is recommended that remelting be performed in a heated water bath or ▲by other suitable methods that will not compromise media quality.▲ (USP 1-Aug-2022) The use of microwave ovens and heating plates is common, but care should be taken to avoid damaging media by overheating and to avoid the potential injury to laboratory personnel from glass breakage and burns. ▲It is recommended that▲ (USP 1-Aug-2022) molten agar medium be held in a monitored water bath ▲until it has been tempered to▲ (USP 1-Aug-2022) 45°–50°, ▲and not further held▲ (USP 1-Aug-2022) for ▲▲ (USP 1-Aug-2022) more than 8 h, ▲or as determined appropriate for the medium composition.▲ (USP 1-Aug-2022) Caution should be taken when pouring the media from a container immersed in a water bath to prevent water from the bath commingling with the poured sterile media. ▲Careful wiping of▲ (USP 1-Aug-2022) the exterior of the container dry before pouring ▲is recommended.▲ (USP 1-Aug-2022)

Disposal of used cultured media (as well as expired media) should follow local biological hazard safety procedures.

Quality Control Testing

Although growth media can be prepared in a laboratory from individual components, many laboratories, for ▲convenience,▲ (USP 1-Aug-2022) use dehydrated media or purchase commercially prepared media in plastic plates or glass containers. Manufacturers of media attempt to standardize raw materials from biological sources but must constantly deal with unavoidable differences in raw materials obtained from natural sources, and therefore lot-to-lot variability of media must be considered. In addition, the performance of media prepared in a laboratory or by a manufacturer is highly dependent on preparation and storage conditions. Improper media preparation can cause unsatisfactory conditions for microbial growth or recovery and unreliable results.

Therefore, quality control tests should be performed on all prepared media, including media associated with swabs or media in strips ▲▲ (USP 1-Aug-2022) . Tests routinely performed on in-house prepared media should include pH, growth promotion, inhibition, and indicative properties (as appropriate). Periodic stability checks to confirm the expiration dating ▲are recommended only until media expiry has been validated.

When media has not been terminally sterilized in its final container and secondary packaging (e.g., irradiated plates of media), an inspection for absence of microbial contamination is recommended for plated or liquid media in tubes to prevent unintended use of contaminated media. The sterility inspection can be performed on a representative sample of the specific media-and-container combination(s) on the basis of the risk of impact on its use in microbiological control testing. The intent of the inspection should be to detect evidence of growth in the relevant medium, such as turbidity in liquid broth media or colonies forming on plated media. Similar to the practice of pre-incubation of non-irradiated, plated media before use in an aseptic manufacturing area, media incubation should be performed at the same temperature range and for at least the maximum time period for which the media is to be incubated in the test (e.g., if incubation time is 3–5 days in the test, the minimum incubation time should be 5 days).

Every in-house sterilized batch of media should be tested for growth promotion.▲ (USP 1-Aug-2022) Test organisms may be selected from the appropriate compendial test chapter. In addition, microorganisms used in growth-promotion testing may be based on the manufacturer's

recommendation for a particular medium or may include representative environmental isolates (but these latter ▲isolates▲ (USP 1-Aug-2022) are not to be construed as compendial requirements).

▲It is commonly stated that a satisfactory growth-promotion outcome includes growth that is visibly comparable to that obtained with a previously tested and approved batch of medium. This is for a qualitative comparison; the comparison medium should be of the same formula, consistency, and volume. If quantitative comparison is desired, follow guidance in *Validation of Microbial Recovery from Pharmacopeial Articles ⟨1227⟩*; the medium should be of the same formula, consistency, and volume. For qualitative and quantitative comparison, direct physical comparison with a previously tested batch is not necessary. Numerical results comparison in quantitative testing should be appropriate for the intended purpose, with adequate knowledge of microbiological growth variability (i.e., factor of 2).▲ (USP 1-Aug-2022)

Expiration dates on media should have supporting growth-promotion testing to indicate that the performance of the media still meets acceptance criteria up to and including the expiration date. The length of shelf life of a batch of media will depend on the stability of the ingredients and formulation under specified conditions, as well as the type of container and closure.

When a batch of media does not meet the requirements of growth-promotion testing, an investigation should be initiated to identify the cause. This investigation should include a corrective action plan to prevent the recurrence of the problem. Any batch of media that fails growth-promotion testing is unsuitable for use. [NOTE—Failed growth-promotion test results may not be used to negate positive test results.]

Some reagents are used for diagnostic purposes to help support identification of ▲microorganisms,▲ (USP 1-Aug-2022) e.g., Gram stain, ▲▲ (USP 1-Aug-2022) oxidase, ▲and coagulase test▲ (USP 1-Aug-2022) reagents. These may have attributes that can be quality control tested similar to microbiological media. Select the correct quality control standard microorganisms, following the manufacturer's instructions, and perform the testing before unknown sample diagnostic testing. All relevant diagnostic reagents should be subjected to incoming quality confirmation before use.

Special care should be taken with media that are used in sterility tests (see *Sterility Tests ⟨71⟩* for requirements) and in environmental monitoring studies. Media used for environmental monitoring of critical areas should preferably be double wrapped and terminally sterilized. If terminal sterilization is not performed, media should be subjected to 100% pre-incubation and inspection before use within a critical area. [NOTE—Growth-promotion testing for this media ▲should▲ (USP 1-Aug-2022) be performed ▲to qualify that▲ (USP 1-Aug-2022) pre-incubation ▲does not impact recovery.▲ (USP 1-Aug-2022)] This will prevent extraneous contamination from being carried into controlled environments and will prevent false-positive results. A raised agar level for surface contact plates should be verified.

Add the following:

▲MICROBIOLOGICAL MEDIA INCUBATION TIMES

Incubation times for microbiological tests with a duration of less than 3 days should be expressed in hours: e.g., “Incubate at 30°–35° for 18–72 h”. Tests with a duration longer than 72 h should be expressed in days: e.g., “Incubate at 30°–35° for 3–5 days”. For tests with incubation times expressed in hours, incubate for the minimum specified time and exercise good microbiological judgment when exceeding that time. For tests with incubation times expressed in days, incubations started in the morning or afternoon should generally be concluded at that same time of day *in the morning or afternoon, respectively*.▲ (USP 1-Aug-2022)

Change to read:

MAINTENANCE OF MICROBIOLOGICAL CULTURES

Biological specimens can be the most delicate standards to manage because their viability and characteristics are dependent on adequate handling and storage. Standardizing the handling and storage of cultures by the user laboratory should be done in a way that will minimize the opportunity for contamination or alteration of growth characteristics. The careful and consistent treatment of stock cultures is critically important to the consistency of microbiological test results. Cultures for use in compendial tests should be acquired from a national culture collection or a qualified secondary supplier ▲and have documented equivalency to relevant ATCC strains (2).▲ (USP 1-Aug-2022) They can be acquired frozen, freeze-dried, on slants, or in ready-to-use forms. Confirmation of the purity of the culture and the identity of the culture should be performed before its use in quality control testing. Ready-to-use cultures should be subjected to incoming testing for purity and identity before use. The confirmation of identity for commonly used laboratory strains ideally should be done at the level of genus and species.

Preparation and resuscitation of cultures should follow the instructions of the supplier or a validated, established method. The “seed-lot technique" is recommended for storage of stock cultures.

The original sample from the national culture collection or a qualified secondary supplier is resuscitated and grown in an appropriate medium. Aliquots of this stock culture (the first transfer or passage) are suspended in a cryoprotective medium, transferred to vials, and frozen at −30° or below until use. If stored at −70° ▲or below,▲ (USP 1-Aug-2022) or in lyophilized form, strains may be kept indefinitely. These frozen stocks can then be used to inoculate monthly or weekly working cultures. Once opened, do not refreeze unused cell suspensions after culturing a working suspension. The unused portion should be discarded to minimize the risk of loss of viability and contamination of the stock.

The number of transfers of working control cultures should be tracked to prevent excessive subculturing that increases the risk of phenotypic alteration or mutation. The number of transfers allowable for specific compendial tests may be specified in that test. One

passage is defined as the transfer of organisms from a viable culture to a fresh medium with growth of the microorganisms. Any form of subculturing is considered to be a transfer/passage.

Change to read:

LABORATORY EQUIPMENT

Most equipment (incubators, water baths, and autoclaves) are subject to standard validation practices of ▲installation▲ (USP 1-Aug-2022) qualification, operational qualification, and performance qualification. ▲Some useful guidance can be found in *Analytical Instrument Qualification* ⟨1058⟩.▲ (USP 1-Aug-2022) Additionally, periodic calibration (generally annually ▲or on a frequency based on a risk assessment▲ (USP 1-Aug-2022)) is commonly required. New equipment, critical to the operation of the laboratory, should be qualified according to a protocol approved by the quality assurance unit (QAU). In addition, regular cleaning and sanitization of equipment such as incubators, refrigerators, and water baths should be performed to minimize the potential for contamination in the laboratory. Door seals of incubators and refrigerators should be cleaned and checked for state of repair. ▲These activities should be incorporated into the equipment preventative maintenance program.▲ (USP 1-Aug-2022)

Instruments (pH meters and spectrophotometers) used in a microbiology laboratory should be calibrated on a regular schedule and tested to verify performance on a routine basis. The frequency of calibration and performance verification will vary based on the type of instrument and the importance of that equipment to the generation of data in the laboratory. ▲Laboratory equipment with software should be evaluated for maintaining data integrity (*Code of Federal Regulations Title 21* (21 CFR), Part 11).▲ (USP 1-Aug-2022)

Equipment that is difficult to sanitize (such as refrigerators and incubators) should be ▲segregated from▲ (USP 1-Aug-2022) aseptic operations (such as storage of media for testing and incubation of sterility test samples) and live culture operations to minimize the potential for inadvertent contamination of the tests.

Autoclaves are central to the operation of the laboratory and must have proper validation in place to demonstrate adequate sterilization for a variety of operations. Autoclave resources must be available (and validated) to sterilize waste media (if performed in that laboratory) as well as the media prepared in that laboratory. The choice of one or several autoclaves is not driven by a need to separate aseptic and live operations (everything in the properly maintained autoclave is sterile after the cycle), but rather driven by resource considerations (see below).

Add the following:

▲USING MODERN TECHNOLOGIES

The use of new technologies in a microbiology laboratory requires new learning and training to ensure a proper implementation in the laboratory (for examples, see *Validation of Alternative Microbiological Methods* ⟨1223⟩, *Microbial Characterization, Identification, and Strain Typing* ⟨1113⟩), and *Rapid Microbial Tests for Release of Sterile Short-Life Products: A Risk-Based Approach* ⟨1071⟩. In addition to the laboratory specialists, the laboratory supervisors or quality assurance personnel evaluating qualification of systems or deviations must also have the skills to analyze and interpret the complex data that may be generated by new techniques. For each new technology, it is valuable to develop rules and principles that will build consistency and accuracy when laboratory personnel are using that technology to perform the relevant procedure. The rules and principles should be included in the written procedure.▲ (USP 1-Aug-2022)

Change to read:

LABORATORY LAYOUT AND OPERATIONS

Laboratory layout and design should carefully consider the requirements of good ▲▲ (USP 1-Aug-2022) practices ▲in a microbiology laboratory▲ (USP 1-Aug-2022) and laboratory safety. It is essential that cross-contamination of microbial cultures ▲or DNA/RNA samples for PCR testing▲ (USP 1-Aug-2022) be minimized to the greatest extent possible, and it is also important that microbiological samples be handled in an environment that makes contamination highly unlikely.

In general, a laboratory should be divided into clean or aseptic areas and live culture areas. Areas in which environmental ▲and other microbiological test▲ (USP 1-Aug-2022) samples are handled and incubated should be maintained completely free of live cultures, if possible. If complete separation of live and clean culture zones cannot be accomplished, then other barriers and aseptic practices should be employed to reduce the likelihood of accidental contamination. These barriers include protective clothing, sanitization and disinfection procedures, and ▲containment by▲ (USP 1-Aug-2022) biological safety cabinets designated for clean or aseptic operations only. Procedures for handling spills or mishaps with live cultures ▲or DNA/RNA▲ (USP 1-Aug-2022) should be in place, and all relevant technical personnel should be trained regarding these methods.

Some samples will demonstrate microbial growth and require further laboratory analysis to identify the contaminants. When growth is detected, the sample should be taken from the clean section of the laboratory to the live culture section without undue delay. Subculturing, staining, microbial identification, or other investigational operations should be undertaken in the live culture section of the laboratory. If possible, any sample found to contain growing colonies should not be opened in the clean zone of the laboratory. Careful segregation of contaminated samples and materials will reduce false-positive results.

Staff engaged in sampling activities should not enter or work in the live culture handling section of a laboratory unless special precautions are taken, including wearing ▲dedicated▲ (USP 1-Aug-2022) protective clothing ▲that should not be worn outside the laboratory (e.g., coats)▲ (USP 1-Aug-2022) and gloves and carefully ▲washing and▲ (USP 1-Aug-2022) sanitizing hands upon exiting. Ideally, staff assigned to sampling activities, particularly those in support of aseptic processing, should not work in the vicinity of live culture laboratory operations.

It is important to consider that microbial contamination of samples, which leads to false-positive results, is always possible unless careful aseptic precautions are taken. Facilities should be designed so that raw material and excipient sampling can be done under controlled conditions, including proper gowning and the use of sterilized sampling equipment. It may not always be possible to sample utility systems, such as water systems, under full aseptic conditions; however, it should be noted that when samples are not taken aseptically, their reliability is inevitably compromised.

Environmental sampling methods should require minimal aseptic handling in loading and unloading sampling instruments. Whenever possible, sampling equipment should be loaded with its microbiological recovery media in the environment that is to be sampled.

All testing in laboratories used for critical testing procedures—such as sterility testing of final dosage forms, bulk product, seed cultures for biological production or ▲PCR testing of▲ (USP 1-Aug-2022) cell cultures used in biological production—should be performed under controlled conditions. ▲Sterility tests should preferably be carried out in an isolator with ISO 5 classification.▲ (USP 1-Aug-2022) Isolators have been shown to have lower levels of environmental contamination than manned clean rooms and, therefore, are generally less likely to produce false-positive results. Proper validation of isolators is critical both to ensure environmental integrity and to prevent the possibility of false-negative results due to chemical disinfection of materials brought into or used within isolators (see *Sterility Testing—Validation of Isolator Systems* ⟨1208⟩). ▲Adequate disinfection of materials prior to loading a sterility test isolator is another important step to reduce the possibility of false-positive results.

For less-critical microbiological testing, such as with nonsterile product or intermediate bioburden samples, testing under a unidirectional airflow (UDAF) cabinet, or as applicable is preferable. During qualification, the UDAF air must meet the air quality grade for which it is being qualified. In addition to the qualification, the cabinet's environment (air and surfaces) may be tested periodically. The testing frequency and levels defined would depend on the microbiological grade of the product tested, the quality of air that can be delivered by the UDAF design and filters, the fact that nonsterile material may be present in the UDAF and the cleaning/disinfection regime.▲ (USP 1-Aug-2022)

Change to read:

SAMPLE HANDLING

Viable microorganisms in most microbiology samples—particularly water, environmental monitoring, and bioburden samples—are sensitive to handling and storage conditions. Critical parameters in these conditions include product (or sample) composition, container composition, time of storage, and temperature of storage. Therefore, it is important to minimize the amount of time between the sampling event and the initiation of testing and to control, as much as possible, the conditions of storage. ▲Microbiological samples should never be stored in a frozen state before testing because this practice leads to loss of cell viability.▲ (USP 1-Aug-2022) If the sample is to be transported to a distant location for testing, then the conditions of transport (time, temperature, etc.) should be qualified as suitable for that test and sample. ▲For example, when monitoring water or bioburden prior to bioburden-reducing steps or sterilizing steps, samples may be held at 2°–8° for up to 24 h from the time of sample collection until the start of the analysis (3). When testing within 24 h is not possible (e.g., when contract laboratories are used), the actual maximum hold time between collection and testing should be supported by experimental studies (e.g., challenge tests). For bacterial endotoxin testing, studies may be performed to demonstrate that endotoxins present in the product and stored in the original container for a certain time may be adequately recovered. Storage conditions (e.g., 2°–8°) in the laboratory should apply. Highly purified lipopolysaccharides (LPS) such as reference standard endotoxins (RSE) or control standard endotoxins (CSE) might not be the most relevant endotoxin indicators for such studies and use of laboratory-derived endotoxin indicators would provide a more realistic assessment as discussed in *Endotoxin Indicators for Depyrogenation* ⟨1228.5⟩.

If environmental monitoring samples cannot be incubated within a reasonable time frame (e.g., due to the use of an off-site testing laboratory), the time from sample collection to the start of incubation should be supported with experimental data.

All samples should be examined and the tests completed prior to release, whenever possible.▲ (USP 1-Aug-2022)

Product mixing before sampling may need to be evaluated and applied ▲▲ (USP 1-Aug-2022) to ensure ▲adequate dispersal▲ (USP 1-Aug-2022) and representation in the sample aliquot.

All microbiological samples should be taken using aseptic techniques, including those taken in support of nonsterile products. If possible, all microbiological samples should be taken under full aseptic conditions in specialized sampling areas. The areas ▲and methods of transport of samples should be designed▲ (USP 1-Aug-2022) to minimize contamination▲▲ (USP 1-Aug-2022) .

Samples submitted to the microbiology laboratory should be accompanied by documentation detailing source of the sample, date the sample was taken, date of sample submission, person or department responsible for the submission, ▲storage conditions,▲ (USP 1-Aug-2022) and any potentially hazardous materials associated with the sample. The testing department should acknowledge receipt of the sample and reconcile the identity and number of samples as part of this sample documentation.

Delete the following:

▲MICROBIOLOGICAL MEDIA INCUBATION TIMES

Incubation times for microbiological tests of less than 3 days' duration should be expressed in hours: e.g., “Incubate at 30° to 35° for 18 to 72 hours”. Tests longer than 72 hours' duration should be expressed in days: e.g., “Incubate at 30° to 35° for 3 to 5 days”. For incubation times expressed in hours, incubate for the minimum specified time, and exercise good microbiological judgment when exceeding the incubation time. For incubation times expressed in days, incubations started in the morning or afternoon should generally be concluded at that same time of day.▲ (USP 1-Aug-2022)

Add the following:

▲INCUBATION TEMPERATURE EXCURSIONS

Incubation equipment qualification and ongoing calibration provide the acceptable range for temperature conditions relative to the expected procedural incubation temperatures or range. When an excursion occurs outside of the procedural incubation temperature(s), an assessment should be performed to determine the potential impact on the test samples and what, if any, action should be taken with the test samples. The effect of a higher or lower temperature on microbial recovery from the test samples for the recorded period of time should be evaluated. An investigation of the excursion should be documented along with the disposition of the test samples. For instance, a slightly lower temperature excursion (e.g., 1°–2°) for a brief time could be compensated with an increase in incubation time; or, for a higher temperature excursion (e.g., greater than 40° for a total aerobic microbial count or greater than 30° for a total yeasts and molds count) consider any negative impact on recovery.▲ (USP 1-Aug-2022)

Change to read:

▲COMPETENCIES AND▲ (USP 1-AUG-2022) TRAINING OF PERSONNEL

Each person engaged in each phase of pharmaceutical manufacture should have the education, training, and experience to do his or her job. The demands of microbiological testing require that the core educational background of the staff, supervisors, and managers be in microbiology or a closely related biological science. They should be assigned responsibilities in keeping with their level of skill and experience.

A coherent system of standard operating procedures (SOPs) is necessary to run the microbiology laboratory. These procedures serve two purposes in a training program. Firstly, these SOPs describe the methodology that the microbiologist will follow to obtain accurate and reproducible results, and so serve as the basis for training. Secondly, by tracking the procedures in which a particular microbiologist has demonstrated proficiency, the procedure number or title also serves to identify what training the microbiologist has received specific to his or her job function.

Training curricula should be established for each laboratory staff member specific to his or her job function. He or she should not independently conduct a microbial test until qualified to run the test. Training records should be current, documenting the microbiologist's training in the current revision to the particular SOP.

▲Performing USP microbiology methods requires a quality control infrastructure that will support accuracy and consistency of method outcomes. While this chapter provides information about effective microbiology practices, there are other *USP* chapters that offer guidance in relevant areas where microbiology is integrated (see *Guide to General Chapters* and *Chapter Charts*).▲ (USP 1-Aug-2022)

Periodic performance assessment is a wise investment in data quality. This performance testing should provide evidence of competency in core activities of the microbiology laboratory such as hygiene, plating, aseptic technique, documentation, and others as suggested by the microbiologist's job function.

Microbiologists with supervisory or managerial responsibilities should have appropriate education and in-house training in supervisory skills, laboratory safety, scheduling, budgeting, investigational skills, technical report writing, relevant SOPs, and other critical aspects of the company's processes as suggested in their role of directing a laboratory function.

Competency may be demonstrated by specific course work, relevant experience, and routinely engaging in relevant continuing education. Achieving certification through an accredited body is also a desirable credential. Further, it is expected that laboratory supervisors and managers have a demonstrated level of competence in microbiology at least as high as those they supervise. Expertise in microbiology can be achieved in a variety of ▲ways▲ (USP 1-Aug-2022) in addition to academic course work and accreditation. Each company is expected to evaluate the credentials of those responsible for designing, implementing, and operating the microbiology program. Companies can thus ensure that those responsible for the program understand the basic principles of microbiology, can interpret guidelines and regulations based on good science, and have access to individuals with theoretical and practical knowledge in microbiology to provide assistance in areas in which the persons responsible for the program may not have adequate knowledge and understanding. It should be noted that microbiology is a scientifically based discipline that deals with biological principles substantially different from those of analytical chemistry and engineering disciplines. Many times it is difficult for individuals without specific microbiological training to make the transition.

Add the following:

▲QUALIFICATION OF ANALYSTS

The hiring of experienced personnel combined with periodic training and qualification of analysts, including regular vision checks, should limit to an acceptable level the variability of microbiological test results produced by each analyst's handling and reading of test results, as well as ensure that the defined good documentation practices are understood and followed.

These also apply to personnel who may be involved in visual inspection of media fill units.▲ (USP 1-Aug-2022)

Add the following:

▲CONSIDERATIONS FOR MICROBIOLOGICAL RISK ASSESSMENTS

A microbiological risk assessment can be beneficial and provide information to assist in decision-making about the impact of microbiological quality concerns. (See *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩ for additional specific parameters for evaluating non-specified microorganisms that may be present in nonsterile products.)

Some examples of when a microbiological risk assessment might be used are: 1) elevated bioburden counts (but within specification); 2) growth of atypical colonies after enrichment on selective agar plates for compendium-specified microorganisms; 3) exceeded alert/action levels; and 4) identification of a recovered species of concern.

The nature and intent of a risk assessment can differ depending on the relevant situation. The following is a list of example topics that could be included as part of the risk assessment.

- **Scope of the Event—**Providing information on the number of product lots that are directly or indirectly impacted on the basis of shared raw materials, shared equipment, and similar manufacturing processes.
- **Microorganism Identification—**Identifying the microorganism(s) to the species level whenever possible.
- **Characterization and Source of the Microorganism(s)—**Researching the literature to determine where the natural habitat for the microorganism can be found; the potential physiological states for the microorganism (e.g., spore vs. vegetative, planktonic vs. biofilm); and the potential pathogenicity of the species, the disease potential of the microorganism for the intended route of administration, and the number of microorganisms recovered.
- **Manufacturing Process—**Evaluating the product/material manufacturing process (or for an API or raw material) to determine if it contains microbial ingress and/or growth-control points or growth-promoting, or microbial-reducing steps.
- **Target Patient Base and Intended Use of the Product(s)—**Identifying potential health effects to the probable user group(s) targeted by the product based on the product insert and label information.
- **Route of Administration of the Product(s)—**Identifying the route of administration of the product (e.g., oral non-aqueous/aqueous, topical, inhalant, etc.). If it is an API or raw material, identify the route of administration of the product that it will be used to manufacture.
- **Intrinsic Product(s) Characteristics—**Evaluating the intrinsic characteristics of the product and the effect they could have on the level of microorganism(s) over shelf life. This means identifying the nature of the product (such as its water activity or pH) and whether the product can support growth or has antimicrobial activity.
- **Assessment Conclusion—**Providing a sound, scientifically-based determination. For example, determination that a microorganism is objectionable or is not objectionable in the test article.

The risk assessment should include determination of the level of risk to the patient or product for an impacted material that is used to manufacture finished product(s) or for a finished product that will be released to the market. An investigation to determine the source of a recovered species of concern and its contamination risk may be required to be completed before a drug product is released to the market. Writing and approval of a microbiological risk assessment should be performed by personnel with specialized education and experience in microbiology.▲ (USP 1-Aug-2022)

Change to read:

LABORATORY RESOURCES

The laboratory management is responsible for ensuring that the laboratory has sufficient resources to meet the existing testing requirements ▲(*4*).▲ (USP 1-Aug-2022) This requires some proficiency in budget management and in determining appropriate measures of laboratory performance. A measure of laboratory performance is the number of investigations performed on tests conducted by the laboratory, but this measure alone is not sufficient. In addition to tracking investigations, the period of time between sample submission and initiation of testing should be tracked, as well as the period of time between end of test and report release (or test closure). Significant delays in these measures are also indications of an under-resourced laboratory staff.

The laboratory management should have sufficient budget to meet testing requirements. Particular measures of budgetary requirements will be specific to the given laboratory, but budgetary considerations related directly to the need of the laboratory for sufficient resources must be addressed to ensure reliable testing results ▲(*4*).

Oversight of Contract Laboratories

Some companies do not have the laboratory space, specialized equipment, or capacity to conduct high-volume microbiological analyses, so they may outsource this type of testing to contract laboratories. It is the company's responsibility to thoroughly investigate the reputation and quality control performance of any new or unfamiliar contract laboratory with which they engage in a quality agreement. Before signing an agreement, a manufacturer should confirm that the contract laboratory complies with current good manufacturing practice (GMP) regulations regarding laboratory qualifications, can perform the required USP compendial testing for microbial recovery and bacterial endotoxins (see *Tests for Burkholderia Cepacia Complex* ⟨60⟩, *Microbial Enumeration Tests* ⟨61⟩, *Tests for Specified Microorganisms* ⟨62⟩, ⟨71⟩, and *Bacterial Endotoxins Test* ⟨85⟩), and an onsite audit can be conducted or, perhaps, a sample batch submitted for testing to ensure the

quality of testing and data integrity. The qualifications of the laboratory management staff to interpret microbiological sample results need to be documented, especially if these staff will serve as subject matter experts for data review or if a laboratory investigation of questionable sample results ever needs to be conducted. Reports written by the contract laboratory should include complete analytical worksheets from the analysis performed. The raw data should be available to and periodically reviewed by a qualified microbiologist of the client company in order to verify the reliability of finished work. All the data used for calculations, including all the positive (growth-promotion results) and negative controls used during analysis, should also be included in the final report. In contrast, a certificate of analysis with a summary of analytical results does not provide all the information needed to verify sample test data or satisfy a regulatory audit. Relevant method-suitability test results should also be available to support the subsequent testing.

Oversight of Suppliers

The impact of the microbiological quality of materials from a supplier can be significant for the laboratory (e.g., media, reagents, cultures) or for manufacturing (e.g., excipients, components); thus, microbiology knowledge and experience is critical for adequate oversight of a supplier. Since the microbiology laboratory can perform specification tests for excipients and products, alignment of knowledge and understanding with a supplier is valuable. Based on evaluation of the appropriate microbiological quality for each material, adequate supplier oversight from a microbiological perspective can provide increased knowledge, with consistent quality of the materials, and improved trust in the relationship with the supplier. For the laboratory supplies, materials of good quality are an important input to systematically maintain laboratory capability for performing consistent tests. For the manufacturing operations, an excipient supply of good quality provides the foundation for a consistently produced product that is microbiologically safe for patients. The full understanding and evaluation of a supplier's microbiological testing strategy, along with sampling, test methodology, and training, provides a means for developing a relationship with transparency and integrity. An experienced microbiologist should initiate ongoing communications in this type of customer–supplier relationship and serve as a technical expert. The controls in place for testing and inspection of incoming lab supplies are key to supply control.▲ (USP 1-Aug-2022)

Add the following:

▲METHOD TRANSFER

Performance of validated methods can change from one laboratory to another. Differences in media, reagents, equipment, procedures, and in levels of experience of personnel can all affect the outcome of a microbiological method. When transferring a method from one laboratory to another, control of the change should be evaluated and directed so that there is minimal negative impact. Each combination of method and test substance should be performed, according to the requisite procedure, by both the sending and receiving laboratories in an appropriately defined and documented activity (with a defined number of replicates) that will ensure that method testing capability and experience have been transferred effectively.

For method transfers, comparative testing of the same sample may not be relevant for microbiological methods due to the non-homogeneity of microbial cells in the sample. Since no contamination is frequently observed, such testing would result in comparing zero counts. Carrying out a method suitability verification of the analytical method of the product to be transferred would provide greater assurance that the transfer-receiving unit may adequately perform the tests under the conditions with the material used (e.g. nutrient media).▲ (USP 1-Aug-2022)

Change to read:

DOCUMENTATION

Documentation ▲(either manually or by an electronic laboratory management system)▲ (USP 1-Aug-2022) should be sufficient to demonstrate that the testing was performed in a laboratory and by methods that were under control. This includes, but is not limited to, documentation of the following:

- Microbiologist training and verification of proficiency
- Equipment validation, calibration, and maintenance
- Equipment ▲monitoring▲ (USP 1-Aug-2022) during test (e.g., 24-h/7-day chart recorders ▲for incubators▲ (USP 1-Aug-2022))
- Media preparation, sterility checks, growth-promotion,▲indicative, and inhibitory▲ (USP 1-Aug-2022) capabilities
- Media inventory ▲quality▲ (USP 1-Aug-2022) control ▲and shelf-life▲ (USP 1-Aug-2022) testing
- Critical aspects of test conducted as specified by a procedure
- Data and calculations verification
- Reports reviewed by QAU or a qualified responsible manager
- Investigation of data deviations (when required)

▲Data integrity guidance will be addressed later in this chapter.▲ (USP 1-Aug-2022)

Change to read:

MAINTENANCE OF LABORATORY RECORDS

Proper recording of data and studies is critical to the success of the microbiology laboratory. The overriding principle is that the test should be performed as written in the SOP, the SOP should be written to reflect how the test is actually performed, and the laboratory notebook should provide a record of all critical ▲information▲ (USP 1-Aug-2022) needed to reconstruct the details of the testing and confirm the integrity of the data. At a minimum, a laboratory write-up should include the following:

- Date
- Material tested
- Microbiologist's name
- Procedure number
- Documented test results
- Deviations (if any)
- Documented ▲significant method steps and▲ (USP 1-Aug-2022) parameters (equipment used, microbial stock cultures used, media lots used)
- Management/Second review signature

Every critical piece of equipment should be ▲documented▲ (USP 1-Aug-2022) in the write-up, and all should be on a calibration schedule documented by SOP and maintenance records. Where appropriate, logbooks or forms should be available and supportive of the laboratory notebook records. Equipment temperatures (water baths, incubators, autoclaves) should be recorded and traceable.

The governing SOP and revision should be clearly noted in the write-up. Changes in the data should be crossed off with a single line and initialed. Original data should not be erased or covered over.

Test results should include the original plate counts, allowing a reviewer to recreate the calculations used to derive the final test results. Methods for data analysis should be detailed in cited SOPs. If charts or graphs are incorporated into ▲paper▲ (USP 1-Aug-2022) laboratory notebooks, they should be secured with clear tape and should not be obstructing any data on the page. The chart or graph should be signed by the person adding the document, with the signature overlapping the chart and the notebook page. Lab notebooks should include page numbers, a table of contents for reference, and an intact timeline of use. ▲Similar requirements should be established for electronic laboratory notebooks that capture this same information.▲ (USP 1-Aug-2022)

All laboratory records should be archived and protected against catastrophic loss. A formal record-retention and -retrieval program should be in place.

Add the following:

▲QUANTITATIVE MICROBIOLOGY

Classical microbiology utilizes the colony forming unit (cfu) as the basis of quantitation for growth-based methods (5). The heterogeneous nature of microbial contamination can lead to inaccuracies in quantitative methods. While representative sampling is a high priority in all methods, calculating colony counts with averaging can lead to subjective and varied results depending on the plate reader and analyst experience. It is important to understand that although averaging colony counts from multiple plates can make the analysis simpler, a wide range of individual plate counts could lead to underestimation of actual contamination. Rounding of cfu, another quantitative principle, should be carefully evaluated for fit with the method to avoid reporting inaccurate results. [Note—Microbial colonies represent biological entities; thus, fractions or decimals in colony count results are meaningless.] There are methods, such as kinetic bacterial endotoxin testing, where decimal place calculations are expected. Be careful of placing too much significance on the decimal portion of a result when evaluating a result compared to an endotoxin limit specification.▲ (USP 1-Aug-2022)

Add the following:

▲DATA INTEGRITY OF MICROBIOLOGICAL DATA

Microbiological methods are classically performed manually and on the basis of visual evaluation by an analyst performing the test. Therefore, the interpretation of test results or the number of colonies tested may be prone to a certain subjectivity and variability. To further improve data integrity and reduce subjectivity, alternative methods for the reading of plates, such as the use of automated plate readers or high-resolution photographs of the plate, may be used. However, these systems can have inherent challenges such as difficulty with the following: counting colonies embedded in the agar gel from pour-plated dishes, counting satellite colonies, differentiating overlapping colonies, differentiating particles from colonies, and interpreting the photo consistently from one individual to another. Automated enumeration methods that stack images to capture colonies growing in time may overcome some of these challenges.

It should be noted that, in order to avoid jeopardizing the asepsis status required during testing, contemporaneous recording of actions during execution of the microbiological testing cannot be followed in all cases. It is acceptable for recording of actions to take place immediately after the working session upon exiting the UDAF hood instead of constantly having to go back and forth from aseptic to non-aseptic areas to write down test actions executed.

Counts from Petri plates are considered original data on the day that the method requires the plates to be read and recorded. After reading, if these same plates are subsequently stored at room temperature or under refrigeration, it is not possible to confirm the original results because the microbial counts may increase during storage. Many microbial colonies continue to grow during refrigeration but at a slower

rate. The colony counts derived from conducting a microbe test using a compendial method depend on adherence to the incubation time and temperature stated in the prescribed method (i.e., ⟨61⟩).

It is common practice for the raw data sheet that contains the original data, as well as the data entry from the raw data sheet to the laboratory information management systems (LIMS), to be reviewed for accuracy and completion by a qualified analyst, an analyst who has not executed or evaluated the test, or the supervisor.

An important data integrity threat with microbiological testing resides with falsification of data and intentional omission of testing results. To control this risk, the company culture and ethical standards are essential as well as the application of a rigorous quality management system.

For the compendial sterility test that combines criticality of the test and higher risk of misinterpretation of results, it is now a standard practice to have a second analyst perform a contemporaneous evaluation of the sample (in test media) for microbial growth. Nonetheless, applying uncritically a contemporaneous reading by a second analyst (four-eyes principle) for all samples and microbiological tests is not recommended. Precision in counts may vary from one analyst to another (even if they are trained and qualified) as colonies may overlap, swarm over media, etc., allowing for misinterpretation. Microbiology is a “logarithmic science” (⟨1223⟩); sample size is statistically weak and testing procedures have inherent variability. By tolerating no differences in counts, a high number of non-critical deviations will be generated, thus consuming resources unreasonably. As an alternative to a contemporaneous enumeration, a contemporaneous verification by a second person that the testing activity is performed correctly may be executed for higher risk tests. A second person could verify, for instance, if the reading of results is correctly executed according to the procedure, if the result on the Petri plate is correctly transcribed onto the GMP recording sheet (i.e., if growth is observed this is captured in the GMP sheet), and if the description of the sample corresponds to the description on the GMP recording sheet. An assessment of the risk due to a misinterpreted result and its impact on patient safety is performed to determine the high risk test outlined above.▲ (USP 1-Aug-2022)

Change to read:

INTERPRETATION OF ASSAY RESULTS

Analytical microbiological assay results can be difficult to interpret for several important reasons: 1) microorganisms are ubiquitous in nature, and common environmental contaminants—particularly organisms associated with humans—predominate in many types of microbiological analysis; 2) the analyst has the potential to introduce contaminating organisms during sample handling or processing in the laboratory; 3) microorganisms may not be homogeneously distributed within a sample or an environment; and 4) microbiological assays are subject to considerable variability of outcome. Therefore, apparent differences from an expected outcome may not be significant.

Because of these characteristics of microbiological analysis, laboratory studies should be conducted with the utmost care ▲(using aseptic techniques)▲ (USP 1-Aug-2022) to avoid exogenous contamination as previously discussed in this chapter. Equally important, results must be interpreted from a broad microbiological perspective, considering not only the nature of the putative contaminant but the likelihood of that organism(s) surviving in the pharmaceutical ingredient, excipient, or environment under test. In addition, the growth characteristics of the microorganism should be considered (especially in questions of the growth of filamentous fungi in liquid media).

▲Microbiological data should be scheduled to be reviewed and trended to assess the capability of the measures to control contamination and ensure the microbiological quality of products or raw materials remains within the acceptance criteria defined and is not worsening. Trending of microbiological data can be performed in several ways, but the end goal is to determine if an adverse trend is arising. An adverse microbiological trend is an early warning of a potential degradation or loss of control within the environment, the utility, raw material, or product tested. Multiple designations may be used to define adverse trends, and it is up to the user to define which is the most relevant definition in the context of the application. For instance, an adverse trend can be defined as repeating higher than usual counts or increasing amount and variety of microorganisms or contamination occurrences over a certain time period. An adverse trend may be systematically related to multiple events.

To reduce the role of subjectivity and to distinguish counts that are out of expectation or that differ from the norm, monitoring levels could be calculated using statistical methods. There is no absolute standard that can be used to calculate levels using historical data as data distribution may differ among the different microbiological tests. Microbiological data are generally not normally distributed, may contain many zero counts (for highly controlled or aseptic areas), and are highly variable. Therefore, classical process control tools based on normally distributed data may not apply. The percentile ranking method using the negative binomial or gamma fit distribution has been shown to be reliable and covers a large diversity of microbiological data (*6*). As an alternative, if enough values are available, a non-parametric fit may be used.

Use of Negative Controls

Some microbiological methods specify the use of a negative control, but their use in other situations should be relevant and appropriate. For example, the testing of rinse fluid without product in a membrane filtration sterility test could provide useful information in a laboratory investigation of an out-of-specification result. Also, for bioburden testing, a negative control can provide ongoing trending of lab equipment sterilization and good aseptic techniques.

Investigations▲ (USP 1-Aug-2022)

When results are observed that do not conform to a compendial monograph or other established acceptance criteria, an investigation ▲▲ (USP 1-Aug-2022) is required. There are generally two distinct reasons for the observation of microbial contamination that does not comply with a target or requirement: A laboratory error or laboratory environmental conditions may have produced an invalid result, or the product

contains a level of contamination or specific types of contaminants outside established levels or limits. ▲In such cases, conduct an investigation using an appropriate investigative tool (e.g., Ishikawa "fishbone" diagrams or the Kepner-Tregoe method).▲ (USP 1-Aug-2022)

Laboratory management and, in most cases, the QAU should be notified immediately. ▲Immediate actions may be required if the product's quality is potentially impacted by the deviation. These may include, for instance, putting the batch in quarantine and assessing the potential impact for batches produced in the same campaign or already released on the market.▲ (USP 1-Aug-2022)

A full and comprehensive evaluation of the laboratory situation surrounding the result should be undertaken. All microbiological conditions or factors that could bring about the observed condition should be fully considered, including the magnitude of the excursion compared to established limits or levels. In addition, an estimate of the variability of the assay may be required to determine whether the finding is significant.

The laboratory environment, the protective conditions in place for sampling, historical findings concerning the material under test, and the nature of the material, particularly with regard to microbial survival or proliferation in contact with the material, should be considered in the investigation. In addition, interviews with the laboratory analyst(s) may provide information regarding the actual conduct of the assay that can be valuable in determining the reliability of the result and in determining an appropriate course of action. If laboratory operations are identified as the cause of the nonconforming test outcome, then a corrective action plan should be developed to address the problem(s). Following the approval and implementation of the corrective action plan, the situation should be carefully monitored and the adequacy of the corrective action determined.

If assay results are invalidated on the basis of the discovery of an attributable error, this action must be documented. Laboratories also should have approved procedures for ▲additional▲ (USP 1-Aug-2022) testing (retesting), and if necessary, resampling where specific regulatory or compendial guidance does not govern the conduct of an assay investigation. ▲Since microorganisms are not necessarily homogeneously distributed in a sample; microbial numbers evolve following storage; all volume of the sample is used during testing in some cases; and sampling is a snapshot of a short time; the classical retesting rules for chemical analysis should not be applied in microbiological testing. Additional testing of the original product, raw materials, intermediates, environment, etc., however, may serve to provide supportive information for the root cause investigation but not be used to invalidate the original results.▲ (USP 1-Aug-2022)

Add the following:

▲REFERENCES

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Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<1117> MICROBIOLOGICAL BEST LABORATORY PRACTICES	Leslie Furr Associate Scientific Liaison	GCM2022 General Chapters - Microbiology 2022

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