CETA Application Guide
CAG-013

Media-Fill Testing for Sterile Compounding Personnel

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Foreword

The Controlled Environment Testing Association (CETA) is an international organization. One of CETA's objectives is to promote quality assurance through the review of existing standards and the development of new methodologies. One of the main vehicles for obtaining this goal is our CETA Application Guides (CAGs). The CETA Application Guides have proven to be an immeasurably valuable tool to a wide variety of professionals in our industry. They have been used by many safety professionals, industrial hygienists, facility engineers and quality control personnel.

The standards and other documents normatively referenced, in whole or in part, in this CETA Application Guide are indispensable for its use and application. The content of this CAG has its origin in material found in these reference documents. Preparation and development of these guides are the outcome of work completed by technical committees that are formed by the CETA Board of Directors.

Abstract

Sterile compounding personnel pose the greatest risk to the microbial integrity of a compounded sterile preparation (CSP) through inherent bioburden and improper or poor technique when preparing and handling CSPs. Media-fill testing evaluates compounding personnel's aseptic technique and ability to safely prepare CSPs for patients.

1 Introduction

The purpose of this guide is to establish an industry-based methodology for complying with the compounding testing in aseptic manipulation delineated in USP Chapter <797> *Pharmaceutical Compounding - Sterile Preparations* and USP Chapter <825> *Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging*. This guide is intended to assist in developing standard operating procedures for a sterile compounding facility's compounding personnel competency program to minimize the risk of contamination of the final CSP. This guide utilizes traditional microbiological methods as indicated in the standards.

The individual State Boards of Pharmacy, Departments of Health, and other inspection agencies enforce the standard or their own versions of the standard. When individual state or agency standards conflict with USP Chapter <797> or USP Chapter <825> the standards which the facility is inspected against must be used and clearly identified in any documentation. The United States Pharmacopeia is updated and revised annually. Verify each year that no changes have been made to relevant chapters before proceeding.

2 Scope

This CETA Application Guide (CAG) is designed to provide a uniform approach for media-fill testing (sampling) to evaluate compounding personnel's aseptic technique in compliance with USP Chapter <797> and <825> standards.

2.1 Limitations

This guide does not cover specific information that the sterile compounding facility may require of an outsourced vendor. The vendor is expected to adhere to the service agreement and applicable facility SOPs.

This guide may not meet the needs of a facility that must comply with the current good manufacturing practices (CGMP).

This guide does not determine the applicable job functions that require media-fill testing for competency in aseptic technique. This is the responsibility of the sterile compounding facility.

This guide does not address all complex compounding scenarios. It is the responsibility of the sterile compounding facility to ensure their media-fill tests reflect compounding processes in their organization.

This guide is for media-fill testing as it relates to determining aseptic technique competency of compounding personnel and does not verify the capability or accuracy of the compounding environment, specific equipment, or processes used to make sterile preparations.

3 Target Audience

Sterile compounding industry professionals.

4 References

For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

4.1 Reference Documents

USP 42-NF 37: USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging (2019). United States Pharmacopeial Convention, Inc., Rockville, MD, US.

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004). U.S. Department of Health and Human Services Food and Drug Administration, Rockville, MD, US.

ISO 17025: General Requirements for the Competence of Testing and Calibration Laboratories (2017). International Organization for Standardization, Geneva, CH.

4.2 Cited Bibliography

The following documents are cited in the guide. They may be obtained from the source of the publication.

USP General Chapter <797>, USP 41-NF 36: Pharmaceutical Compounding—Sterile Preparations (2008). United States Pharmacopeial Convention, Inc., Rockville, MD, US.

The Revision to USP General Chapter <797>, USP 42-NF 37: Pharmaceutical Compounding—Sterile Preparations. (Published June 1, 2019). United States Pharmacopeial Convention, Inc., Rockville, MD, US.

USP General Chapter <61>, USP 42-NF 37: Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests (2019). United States Pharmacopeial Convention, Inc., Rockville, MD, US.

USP General Chapter <1116>, USP 42-NF 37: Microbiological Control and monitoring of Ascetic Processing Environments (2013). United States Pharmacopeial Convention, Inc., Rockville, MD, US.

5 Nomenclature

The following are technical definitions and acronyms for terms used throughout this application guide:

Aseptic - A state of control, void of unwanted microbial contamination.

BSC - Biosafety Cabinet - A partial barrier system that relies on the movement of air to provide personnel, environmental, and product protection.

CSP - Compounded Sterile Preparation

CSTD – Closed System Drug Transfer Device

DCA - Direct Compounding Area

Documentation - Retrievable record of information that provides evidence required by regulatory standards.

Fail – Does not meet the requirements of the test. In the case of media-fill testing, microbial growth results in failure.

Gloved Fingertip Testing - A test to assess the adequacy of aseptic work practices and garbing competency prior to being allowed to prepare CSPs for human and veterinary use and, for more experienced personnel, to maintain their qualifications. Sterile TSA with lecithin and polysorbate 80 contact plates are used to sample the gloved fingertips of compounding personnel after garbing and after completing the media-fill preparation (without applying sterile 70% IPA).

Growth Promotion - A study where an unused liquid media is inoculated with specific microorganisms in specific quantities and compared to an expected number of colony forming units after incubation, normally performed by the manufacturer for the certificate of analysis. See USP <61>.

ISO - International Organization for Standardization

IVLFZ - Integrated Vertical Laminar Flow Zone

Lab Sample Submission Documentation - A form used to relay the necessary data and requirements of an environmental monitoring session from the sample collector to the lab. It may also be used to track possession and relinquishment of samples.

LAFW - Laminar Airflow Workbench - A device that is a type of LAFS that provides an ISO Class 5 or better air quality environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow

Medium (Media) - There are two forms of TSB (liquid, dehydrated) for the purposes of this CAG:

Liquid media (broth) is a sterile combination of water and nutrients intended to replace drug product and diluent during simulated manipulations.

Media may come in a dehydrated, nonsterile form that must be prepared for use as a broth.

The broth is to support growth of potential microbial contaminates which may enter CSPs due to improper techniques.

Media Fill Unit (MFU) - The final sample/samples generated as part of the media-fill test.

Pass - Meets the requirements of the test. In the case of media-fill testing, microbial growth is not observed in the media.

PEC - Primary Engineering Control - A device or zone that provides an ISO Class 5 air quality environment for sterile compounding.

PPE - Personnel Protective Equipment.

RABS - Restricted Access Barrier System - An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations.

Sanitize - To reduce, on inanimate surfaces, the number of microbial life including fungi, viruses, and bacteria.

SCA - Segregated Compounding Area - A designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.

sIPA - Sterile 70% Isopropyl Alcohol (IPA).

SOP - Standard Operating Procedure.

SRPA - Segregated Radiopharmaceutical Processing Area.

TSA - Tryptic Soy Agar.

Turbid or Turbidity - Cloudiness or haziness of a fluid caused by large numbers of microorganisms.

TSB - Tryptic Soy Broth.

USP - United States Pharmacopeia.

6 Materials and Equipment

Sterile microbial growth medium (soybean-casein digest media e.g. TSB) that has been verified to support growth. Nonsterile to sterile compounding requires a dehydrated media.

Compounding facility supplied PPE for nonhazardous and hazardous cleanrooms, SCAs and SRPAs, including appropriately sized gowns/smocks/bunny suits, sterile gloves, face masks, head cover, shoe covers, and beard cover, if applicable.

Containers and compounding equipment as required by the facility's media-fill testing procedure.

Calibrated incubators for incubation of the MFUs. The incubators are required to maintain a temperature range of 20° to 25°C and 30° to 35°C. Dual incubation is required to support bacterial and fungal growth.

7 Precautions/Safety

Garb according to the sterile compounding facility's SOPs.

All materials required for media-fill testing must be cleaned according to the sterile compounding facility's material transfer process SOP.

Use sterile water to reconstitute the dehydrated media used for nonsterile to sterile media-fill testing.

8 Procedures

8.1 General Considerations

Media-fill testing is used to measure the aseptic skill of compounding personnel. In order to be effective, the media-fill testing procedure must represent the most complex and challenging procedures performed in a sterile compounding facility during the most stressful conditions possible. This ensures processes are able to produce a CSP without microbiological contamination. During this test, a microbiological growth medium is substituted for the actual drug components to simulate admixture compounding. It is the responsibility of the sterile compounding facility to review the types of sterile compounding performed and simulate their own

procedure as closely as possible. To mimic the compounding activities, consider the components, equipment, number of manipulations, transfer process, devices, and the final container.

Procedures for a media-fill test need to reflect all aspects of the compounding personnel's daily work routine which may include:

- Automated compounding devices (e.g., repeater pumps)
- Specialty attachments (e.g., CSTDs, enteral connections, manual fluid dispensing system, gravity infusion connections)
- Delays in compounding process (e.g., use of vial roller/mixer, camera approval equipment)
- Diversity of containers (e.g., ampules, varying size vials and bags)
- Simulating manipulations (e.g., reconstitution)
- Transferring of medications to final containers (e.g., syringes, vials, bags)
- Depending on the equipment that personnel use as part of their daily compounding process consider the use of each type and size of PEC in the media-fill process such as BSC, LAFW, RABS, IVLFZ due to the differing airflow characteristics

Any type of CSP final dosage form that personnel could be expected to compound needs to be represented to ensure that all methods can be performed aseptically. The type of final dosage forms normally consist of, but are not limited to vials, IV bags, and syringes. Additionally, any vessel that is submitted to the lab from the media-fill test should have at least 10% of capacity or media added to the container.

The number of testing replicates is at the discretion of the sterile compounding organization. However, more replicates provide greater assurance of process control.

Initial media-fill testing is performed after the successful completion of the facility's didactic education, practical training, and hand hygiene and garbing evaluation. All compounding personnel must be evaluated on their aseptic technique during a media-fill test prior to independently preparing CSPs for patient use.

Ongoing media-fill testing should be performed after the successful completion of the facility's didactic education.

8.2 Media Considerations

Media must be accompanied by a certificate of analysis that documents the results of the quality control testing performed (growth promotion, pH, and sterilization). This testing is completed by the manufacturer and is in addition to and prior to the quality control testing that may be performed at the microbiological lab if required or requested.

Media must be stored according to the manufacturer's instructions. If the media is subjected to temperatures outside the manufacturer's specified range, it must be evaluated before use and discarded if required. For many media manufacturers, media may be used for media-fill testing up to and including the expiration date. For additional information reference the media's instructions for use.

If the organization performs nonsterile to sterile compounding, dehydrated media must be used as part of the media-fill. Dehydrated, nonsterile TSB can be purchased from several

manufacturers. It will also be accompanied by a certificate of analysis; however, there will not be any sterilization information. Follow the manufacturer's preparation instructions. Actual media-fill procedures may vary depending on a sterile compounding facility's protocols and compounded preparations.

8.3 Sampling Frequency

Testing is required initially, and ongoing testing is performed as required by the current version of applicable USP compounding chapters or local regulatory agencies. Additional testing may be done at the discretion of the sterile compounding facility.

8.4 Testing Procedures

Prior to media-fill testing, compounding personnel must be trained on proper cleanroom behavior and aseptic technique for compounding CSPs. Each person tested should be given the media-fill procedure for review prior to testing. Procedures for testing should be clear, concise, and represent the most challenging manipulations performed on a usual compounding day.

Compounding personnel must be observed and evaluated on their aseptic technique and overall cleanroom behavior by a competent evaluator, which may be a member of the sterile compounding facility management. The evaluator must avoid providing step-by-step instructions and technique corrections during the testing process. Occasional utilization of the evaluator as a resource during the media-fill testing process is acceptable assuming the evaluator is normally available to compounding staff for assistance during the work shift.

After media-fill testing is complete, follow organizational SOPs for sealing stoppers and injection ports on the final MFUs.

Label the MFU with the least amount of information required to identify it. This is the minimum amount of information required to be on a MFU, unless this information is referenced through supporting documentation; the compounder's initials, date, and if necessary, the MFU number, e,g., Vial #1, Vial #2. MFUs submitted for incubation are labeled so that they do not obstruct the ability to view and analyze the MFUs.

Each media-fill test procedure must include direction on which materials from the media-fill test require incubation.

8.5 Lab Sample Submission Documentation

When submitting to a lab for incubation and analysis, they will require documentation to track release, receipt, testing parameters, sample identification, and any other pertinent information. Labs may differ slightly in the information required to process the MFUs.

8.6 Transporting Media-Fill Units

After testing is complete, MFUs are kept at room temperature prior to incubation. If shipping MFUs to a lab, ship them with an overnight carrier. There should be a limited amount of time between when the MFUs are taken and when they arrive at the lab for analysis.

MFUs must be repackaged in a manner that prevents them from being compromised during transport. Procedures for shipping should be discussed with the lab receiving the MFUs as each lab may have specific requirements. Place all MFUs in a sealed plastic bag. When shipping or transporting to the lab, securely pack the shipping container with padding such as bubble wrap or filler material to prevent damage to MFUs.

The lab should initiate the testing process the same day of receipt. Any delay in the shipment or testing of the MFUs must be documented and justified. In the event of MFUs being stored or delayed in shipment for an extended amount of time, discuss each situation with the lab and determine if retesting should be performed or if the MFUs are valid.

8.7 Controls

Negative and positive controls should be submitted for each lot of media used during the media-fill test. Controls must stay with the actual test MFUs through the testing and shipping to ensure the media was acceptable prior to testing and was not impacted during transport to the laboratory. In the event controls are not submitted with the MFUs, it is not acceptable to send controls of the same lot separately to the lab for testing. Each lab may have specific requirements for controls.

Negative controls are media containers that have not been opened and are incubated along with the MFUs. Media is suitable if there is no growth of microorganisms. Negative controls that have growth of microorganisms at the end of the incubation period should be investigated to determine whether that lot of media has been contaminated and affected the test results of other media-fill tests.

Positive controls are unopened containers of media that will be inoculated with microbes by the lab (a list of appropriate microorganisms can be found in USP <61>) for growth or no growth result to ensure the media can still support growth after transport to the lab. Positive control testing is not the equivalent to the growth promotion studies outlined in USP <61>, which may be used by the manufacturer for the certificate of analysis testing. A negative media-fill unit may be used as a positive control after incubation.

For sterile compounding facilities that incubate their own MFUs, at a minimum, a negative control should be incubated with the test MFUs.

8.8 Sample Incubation and Analysis

Incubate MFUs in a calibrated incubator at 20°C to 25°C for 7 days. Remove from the incubator, gently swirl each MFU, and inspect all MFUs for signs of visible microbial growth in the media. Then incubate the MFU in a calibrated incubator at 30°C to 35°C for an additional 7 days. Remove from the incubator, gently swirl each MFU, and inspect for signs of visible microbial growth in the media.

If all MFUs from a media-fill test are clear or display no turbidity or other visual manifestations of microbial growth after incubation, this is a passing test.

8.9 Data Expression

Media-fill results are reported based on the appearance of the media, either clear or turbid, and an indication of pass or fail.

8.10 Documentation

The information listed below must be recorded to summarize the testing. The data may be gathered from the lab, third party testing companies, or the sterile compounding facility. This information is used to demonstrate compliance with regulatory agencies (e.g. state board of pharmacy) or accreditation organizations.

- Facility name and address

- Name of person evaluated
- Name of evaluator
- Evaluation date
- Media type, lot numbers, and expiration dates
- Components (empty bags, vials, etc.), lot numbers and expiration dates
- Media certificate of analysis
- Purpose of sampling (initial, ongoing)
- Processing lab name and address
- Date MFUs were received by the lab
- Identification of who reads and documents the results
- Incubation temperatures, dates, and times
- Results of the positive and negative control testing performed by the lab
- Sample Status (Pass/Fail)
- Deviation (e.g., sampling procedure, handling, cleanroom behavior, incubation)
- Signature of sterile compounding facility management or designee and date of review

8.11 Review of Results

Report test results of media-fill testing to the Facility Designated Individual(s) as soon as test results are known. Facility Designated Individuals are responsible for reviewing sample results and the required documentation as listed in section 8.10 “Documentation”.

8.12 Investigation and Remediation of a Media-Fill Failure

Any positive growth result of media-fill testing must be evaluated. Depending on the situation, retraining may be warranted, such as in the case of a new hire having growth in an ongoing media-fill test. This may include a repeat of personnel qualification evaluations as well as review of written test results and any noted infractions during supervised testing carried out previously. It is up to the sterile compounding facility to decide whether personnel may return to compounding before the results of a repeat media-fill test are received. This should be based on the compounder’s experience and past media-fill test results. Suggested order of corrective actions in response to a media-fill test failure are as follows:

- Review of evaluator comments
- Search for external interference
- Retrain
- Retest
- The individual’s ability to compound CSP’s in the event of a failure is left to the discretion of facility management

Recurring failures among multiple compounding staff should prompt a review of training materials, SOPs, PPE, hand hygiene materials and facilities, media and compounding supply lot numbers, and environmental monitoring results. Identification of growth in positive liquid media can prove useful in a root cause analysis.

9 Addresses and Contacts

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