Enhancing Safety: Optimizing Media Fill Testing and Procedures in Your Facilities

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Relevant Financial Relationship Disclosure

- No one in control of the content in this presentation has a financial relationship with an ineligible company

Objectives

- Define Media Fill Testing
- Describe the importance of testing to training sterile compounders
- Identify approaches for determining “the most difficult and challenging aseptic procedures”
- Discuss optimizing patient safety through creating a robust and comprehensive media fill procedure

Abbreviations

Abbreviation	Meaning
HVAC	Heating, Ventilation and Air Conditioning
ISO	International Standards Organization
GFT	Gloved Fingertips and Thumb Sample
CSP	Compounded Sterile Products
PEC	Primary Engineering Control
PNSU	Probability of Non-Sterile Unit
FDA	Food and Drug Administration
ACD	Automated Compounding Devices
USP	United States Pharmacopeia
SOP	Standard Operating Procedures
SCA	Segregated Compounding Area
HD	Hazardous-Drugs
DP	Designated Person
CFU	Colony-Forming Unit
TSB/SDA	Tryptic Soy Broth/Sabourad Dextrose Agar

Assessment Question #1

› Which of the following statements about Media-Fill Testing is NOT true:

A. Media-fill test units should be documented with complete records including preparation, incubation conditions, and results

B. The primary purpose of media-fill testing is to assess the operator's aseptic technique and secondarily to qualify the compounding environment

C. Any visible turbidity or microbial growth on a single test unit constitutes a failure and requires re-training and re-evaluation of operator's aseptic technique

D. Operators are allowed to compound CSPs independently for a short period upon hire before performing a media-fill test

Assessment Question #2

› Which of the following statements about Media-Fill Testing is NOT true:

A. The conditions should reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person

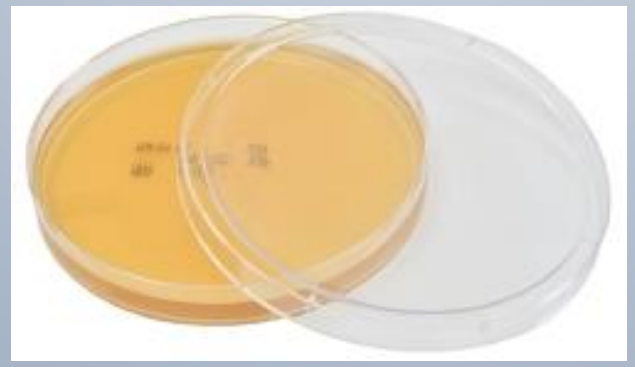
B. Three successful media-fills in succession must occur before personnel are allowed to begin compounding CSP

C. ACDs and other similar equipment are designed to assist in the compounding of preparations should also be involved in a media-fill test if it is routinely part of the compounding process

D. Third-party trainers and microbiology testing of media samples are acceptable to qualify personnel

What are Media Fills/Aseptic Process Simulations?

- Media-Fills or Process Simulations are exercises in which the performance of an aseptic activity is evaluated using a sterile growth medium
  - The medium can be directly substituted for the drug or added to it
- Simulation of the actual aseptic compounding process using a microbial growth medium (typically soybean–casein digest medium, also known as tryptic soy broth (TSB)) instead of the actual drug



Media Fills/Aseptic Process Simulations

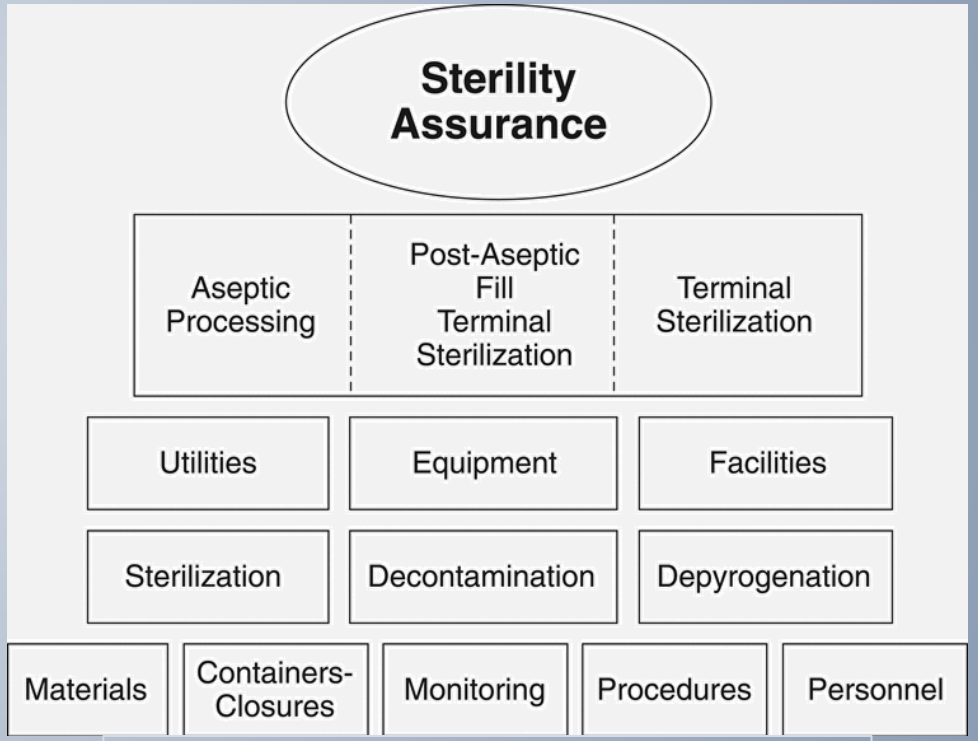
- Aseptic process simulations are typically performed before the introduction of new or revised process components (e.g., products, facilities, equipment, personnel, containers and closures, and processes) and periodically thereafter
- Process simulations should be fully representative of processing conditions and activities utilized during routine production
- Include “worst-case” conditions such as maximum workloads and duration of compounding
  - Use the most difficult and challenging compounding procedures and processing conditions encountered
- If testing accurately simulates the sterile compounding processes, it demonstrates that the process controls and the operator’s aseptic compounding skills are adequate to protect the preparation from contamination

Aseptic Processing of CSPs

- A method by which separate, sterile components (e.g. drugs, containers, or closures) are brought together under conditions that maintain their sterility
- Components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining
  - e.g. using a sterilizing filter
- Where humans are present, microbial contamination is inevitable
- Recognize that even under the best conditions, the probability of contamination isn't 0%
  - Even terminal sterilization has a PNSU of one in a million

Factors on Sterile Preparations Outcomes

- Environment
  - HVAC, ISO Classifications
- Product Flow
  - Personnel and Facility Design
- Cleaning and Maintenance Procedures
- Personnel
  - Hygiene, PPE, Techniques
- Materials Used



USP <1211> Sterility Assurance

Why is Media-Fill Testing Important?

- Qualify personnel engaged in sterile compounding
  - The compounder is the greatest risk to microbial contamination
  - Assures that CSPs can be prepared without contamination
- Qualify processes, the environment and operating controls
  - May serve as Performance Qualification (PQ) in the process validation
- Process selection decision, operation design, process controls, and monitoring systems are essential to provide the necessary **assurance** of establishing the capability to maintain sterility
  - Safety for patients

Personnel Training

- All compounders, designated person and personnel with direct oversight of compounding personnel must complete:
  - Didactic training at least annually
    - Sterile compounding principles and practices
  - Gowning and garbing assessment at least every 6 months
    - Including fingertip samples
      - Every 3 months for Category 3
  - Training and competency in maintaining the quality of the sterile environment
    - Cleaning and disinfecting assessment
  - Media fill testing (with fingertip and surface sampling)
    - At least every 6 months for Category 1 and 2
      - Every 3 months for Category 3
      - Direct oversight annually

Media-Fill Testing Frequency

Personnel Function	Required ⟨797⟩ and Supplemented by Facility SOPs		
	Training and Competency in Sterile Compounding Principles and Practices	**Garbing Competency (Including GFT)**	**Media Fill with Post-GFT and Surface Sampling**
Compounder	At least every 12 months	Category 1 and 2 at least every 6 months Category 3 at least every 3 months	Category 1 and 2 at least every 6 months Category 3 at least every 3 months
Designated person and personnel with direct oversight of compounding personnel	At least every 12 months unless compounding	At least every 12 months unless compounding	At least every 12 months unless compounding

Media-Fill Basics

- Personnel prepare a sterile product using TSB in a way that mimics their usual compounding procedures
- The filled media containers are incubated (typically at 20–25°C for 7 days, then 30–35°C for another 7 days)
- If no microbial growth is observed, the test is “passed”
  - A failed test requires retraining and retesting before the individual is allowed to resume sterile compounding

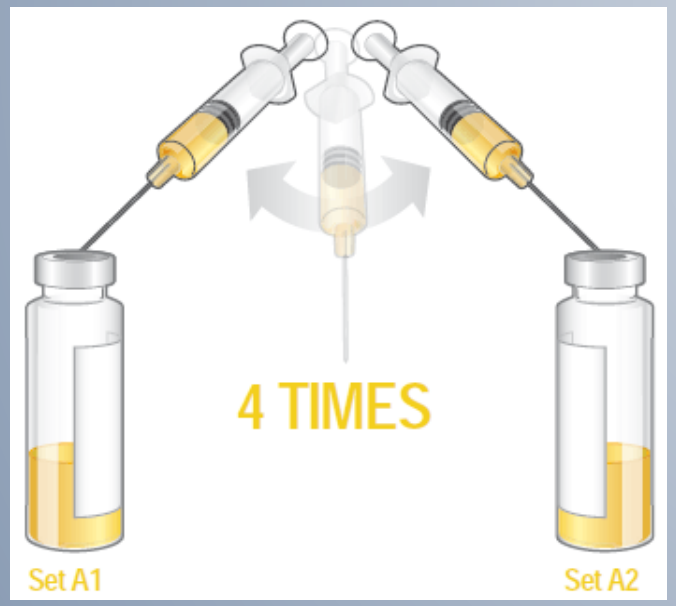
Media Fill Test Design

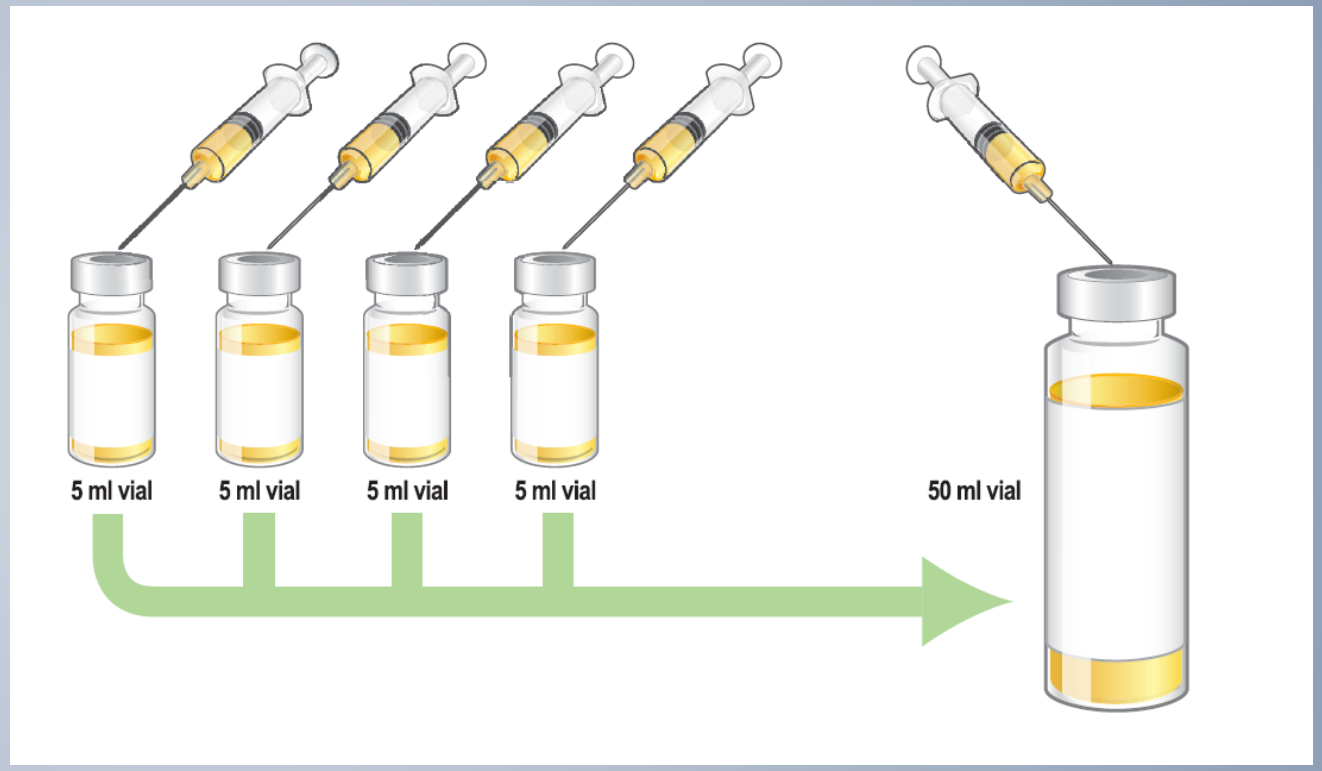
Facility/Organization Type

- Are you both the designated person (DP) and compounder?
  - Consider external training
- Large Companies/Hospital Systems
  - Same DP for all locations?
  - Use personnel in other locations because or call-outs or shortage?
    - Consider having personnel complete media fill across other sites
    - Policies/equipment should be similar throughout systems

MEDIA FILL KITS

May not simulate actual components or processes by facility





483 Media Fill

Failure to conduct media fills that closely simulates aseptic production operations under the worst case, most challenging and stressful conditions.

Specifically,

Your media fill kit of (b) (4) vials of which (b) (4) are positive controls does not simulate your firm's aseptic production operations under the worst case, most challenging and stressful conditions. For example, the following sterile injectable products were produced by the firm:

- On 8/11/2021, (b) (4) aseptically filled vials of Kisspeptin-10 200mcg/ml, Lot 08112021@9, BUD: 12/09/2021.
- On 10/08/2021, (b) (4) aseptically filled vials of Glutathione 200mg/ml, Lot 10082021@12, BUD: 02/05/2022.
- On 10/14/2021, (b) (4) aseptically filled vials of Nandrolone Decanoate 200mg/ml, 10142021@13, BUD: 04/12/2022.

483 Media Fill

OBSERVATION 3

Media fills were not performed that closely simulate aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

Specifically,

a) Your firm did not evaluate any conditions that provide a challenge to aseptic operations as part of the firm's media fill. For example, operators do leave and reenter the ISO 5 area during production; however, this was not addressed in any of the media fills.

Most “Difficult and Challenging”

› The simulation must capture elements that could potentially affect the sterility of the CSP including *but not limited* to:

Elements	Intended to Challenge
• Longest time of a certain manipulation • Most manipulations • Most complex type of preparation • Batch size	Aseptic technique Operator fatigue Quality of equipment used
• Number of personnel in the clean room or SCA • Interruptions • Level of garbing	Increased risk for contamination
• PEC type (horizontal vs. vertical) • Technology and Automation	Aseptic technique Increased risk for contamination Quality of equipment used

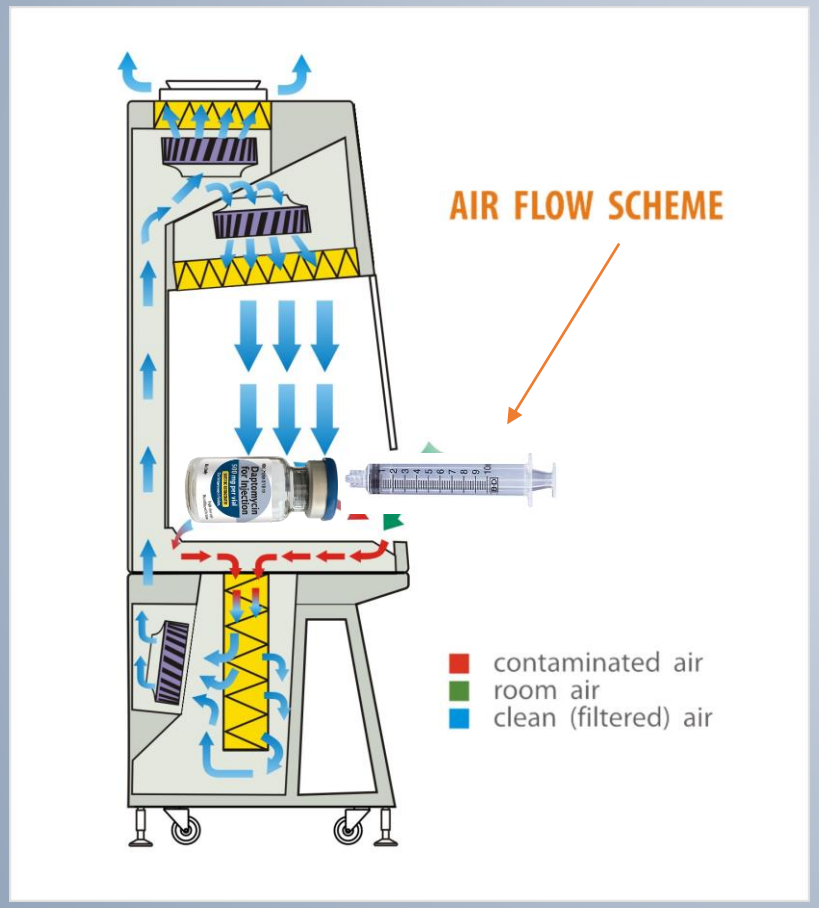
Facility Conditions for Media-Fill Testing

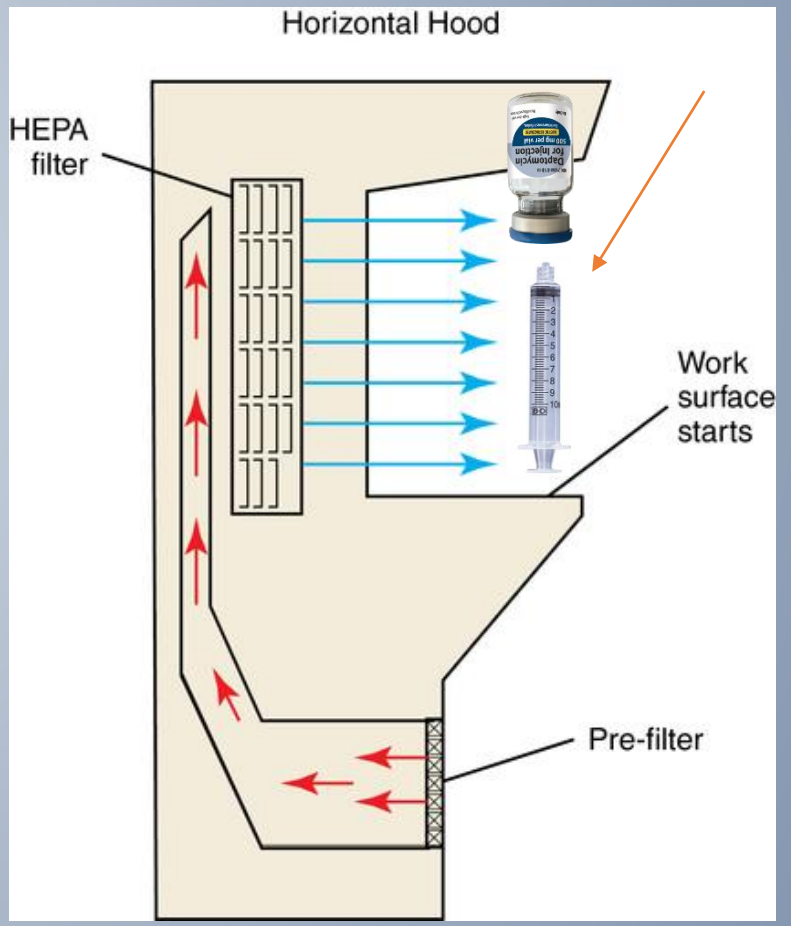
- A media fill should NOT be used to validate bad working practices or events that may pose microbial contamination
  - Compounding facilities shall provide a comfortable and well-lighted working environment, which typically includes a temperature of 20°C or cooler to maintain comfortable conditions for compounding personnel when attired in the required aseptic compounding garb
  - Relative Humidity (RH) < 60%
  - Buffer areas maintain a minimum of 0.020 water column positive pressure, (-0.01 to -0.03 if negative)
- Under <u>dynamic conditions</u>
  - Normal compounding operations when personnel are present and actively involved in the process

Locations of Compounding

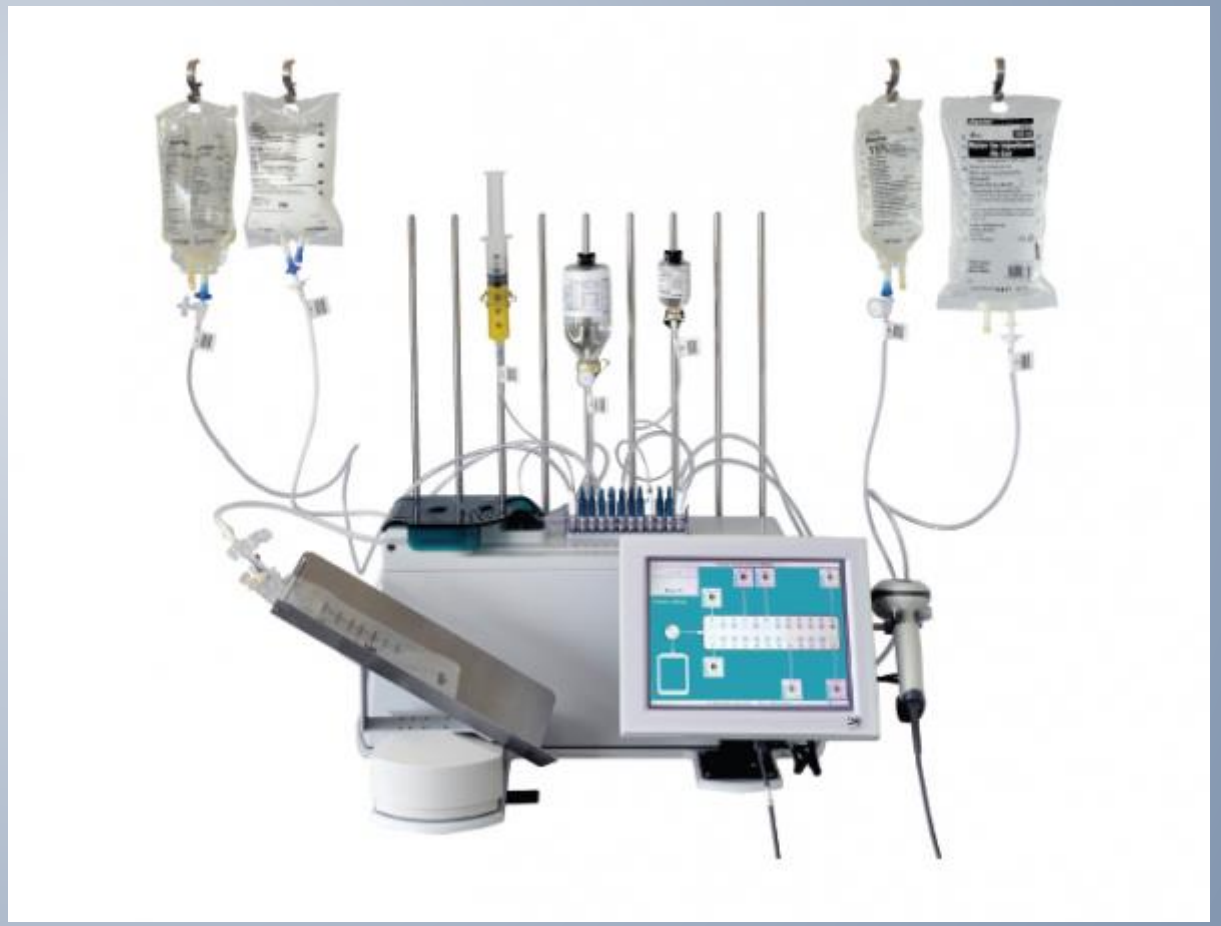
- Does your facility perform in Category 1 (Segregated Compounding Area (SCA)), Category 2 facilities or both?
  - If both, which location is more complex or difficult to compound in?
    - The average amount of personnel in the space in one time
    - More opportunities for contamination (e.g. sinks, open space, doors etc.)
- Wherever the compounder performs the media fill that you deem both most challenging and representative of a typical day, justify the location in the Media-Fill Document
  - "After assessing rooms X, Y and Z, it has been determined that room Y has more compounders in a room at any given time and does not have touchless entry…"
  - "SCA has greatest microbial risk as compared to Category 2 thus…"

DCAs: Vertical Hood vs. Horizontal Hood





Automation (ACD)



Garbing and Gowning

- Media fill participants should wear the most complex attire
  - e.g. if compounders in HD cleanroom wear goggles, non-HD compounders should
- Compounders should wear the facility outlined garb
  - Don't intentionally wear personal clothing, no gloves etc. and say it is "worst-case scenario"
- Hand hygiene should follow standard operating procedures
- If compounders have different garb, justify why this garb most challenging (most likely to cause contamination) and still representative of a typical day, in the media fill document

Compounding Procedure

- What is your most challenging manipulation that can happen in a shift?
  - Ampules are more complex than 2mL vials which are more difficult than 10mL vials etc…
- What is the largest number of CSP one may prepare/longest amount of time sitting during a single preparation?
  - 200 units versus 2 hours in a hood
- Consider a combination of all types of preparations in one media fill test (syringes + bags + eye drops + ACD etc.)

“Challenges” in Procedure – Other Considerations

- Add if they may be common occurrences for extra rigor
  - A glove change to simulate a tear or soiled gloves
  - Compounder gets up to retrieve more supplies in the middle of a preparation to simulate missing items that are needed
  - Compounder doffs garb halfway through the preparation and re-garbs to simulate a restroom or lunch break
  - Compounder stops what they are currently preparing and introduces something else (safely) into the hood to simulate a stat emergency preparation
  - Dropping materials on the floor or producing a minor spill
- Justify the “realistic worst-case” scenarios and their quantities as it pertains to a regular preparation

Media Fill Test Documentation

Testing Requirements (Visual Observation)

- Criteria usually dependent on Standard Operating Procedures
- Can be done in “real-time” or retrospectively (recorded)

Test Type	Action Levels
Garbing and Gowning	Not Acceptable
Cleaning and Disinfecting	Not Acceptable
Aseptic Manipulations	Not Acceptable

Testing Requirements (Procedure)

- A failure in the media fill, gloved fingertip and thumb sampling, or surface sample constitutes an overall failure of the aseptic manipulation competency

Test Type	Action Levels
Media Fill Product(s)	Turbidity or growth in one unit
Gloved Fingertip and Thumb Sampling	>3 cfu total from both hands after media fill
Surface Sampling (DCA)	> 3 cfu

Media-Fill Documentation (Visual-Components)

- Name of person evaluated and evaluator
- Date and time
- Test type
  - Gowning, turbidity, cfu, inspection of components for cracks/leaks aseptic technique etc.
- Evaluator comments and/or corrections
- Results

Media-Fill Documentation (Procedure)

- Name of person evaluated and evaluator
- Date and time
- Simulation process and its justifications
- Components used in process
  - Including manufacturers, lots and expiration dates
- Detailed description of sampling
- Incubation temperatures and durations if done in-house
- Evaluator comments and/or corrections
- Results

Aseptic Process Simulation
Roles and Responsibilities:
Batch Record Creation/Verification: “Name of Supervisor” Name/Date:_____
Execution of Batch: “Name of Operator” Name/Date:_____
Media- Fill Testing: “Pharma Labs” (see attached documentation)

Misc. Information:
Duration: Filling time not to exceed four hours
Acceptance Criteria: 0 contaminated units
Aseptic Process: Filling of sterile solution using Baxa Repeater Pump
Units: No greater than 250 units of 2mL volume
10x10mL growth promotion study samples Royal Blue aluminum flip-off seals

Labels to print: (Theoretical Yield + 10% rounded down to nearest whole number)
_____ Labels Printed: Name/Date:_____
_____ Labels Destroyed Name/Date:_____

NOTE: An extra 250mL is compounded to account for the following:
· 10x10mL vials for the growth promotion study
· 125mL loss during dispensing in two sterile collection bags, two sterile repeater pump tube sets, and one 50mm filter
· 25mL for 0.1mL overfill each vial for a total of 600 vials

*Batch Yield:*_____ *Discrepancy (%):*_____ *Pharmacist:*_____

Equipment and Devices:
Beaker
Hotplate
Stir rod
Sterile Components lot/exp (Operators initial after entry)
Sterile Collection Bag: _____
Sterile Spike(s):_____
Sterile Tubing:_____
Filter:_____
Container Closures _____
Stoppers:_____
Caps (Color, lot, exp):_____
Vials (Clear/Amber, size):_____
Sterile 0.22 micron filter _____
Sterile syringes_____
Sterile needles_____

Formula Instructions:

Preparation of Media for Pre-sterilization Bioburden and Aseptic Process Simulation
In ISO 7 Environment

1. Weigh out TSB powder and place into a depyrogenated beaker. Add approximately 95% of final volume of SWFI and mix using a sterilized spinbar for 60 minutes.
Name/Date/Time:_____

2. Once fully dissolved, check the pH of the solution. pH shall be 7.3 +/- 0.2 at 25° C
Name/Date/Time:_____
pH:_____

3. QS to final volume by adding more SWFI.
Volume before addition:_____Name/Date:_____
Volume of SWFI added:_____Name/Date:_____

4. Using non-sterile tubing, pump solution from beaker, through a Millex-OR or comparable filter, into a sterile collection bag (Bag #1). Withdraw 10mL of volume to simulate the sample taken for pre-sterilization bioburden.

Name/Date/Time:_____

And so on.....

Rationale for "Worst-Case" Scenario:
- No operator is to compound > 250 units in one compounding session
- Procedure mimics a scenario in which depyrogenated vials are not available due to staffing or equipment issues
- Operator must interrupt compounding session at least three times to retrieve more vials from the pass-through, possibly creating turbulent airflow or introducing an item that was not properly staged
- 2mL vials are much more difficult to stopper and seal than larger vials (13mm stoppers and seals as opposed to 20mm stoppers and seals)

Monitoring:
- Complete gloved fingertip test after compounding (change gloves after sampling) and after compounding session.
- Sample four (4) random surfaces of the DCA during and after compounding session
-The “during” sample is taken at the halfway point of a compounding session, e.g. 125 vials completed of a 250-vial batch.
-The “after” sample is taken when the compounding session is complete before the work surface is sanitized

TSA Lot/Expiration Date:_____
SDA Lot/Expiration Date:_____

Notes:
- All vials are to be sent to PharmLabs for analysis.
- Incubation time should not be less than 14 days.
- Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in inspecting media fill units for microbiological contamination. If QC personnel do not perform the inspection, there should be QC unit oversight throughout any such examination.
- All suspect units identified during the examination should be brought to the immediate attention of the QC microbiologist.
- Attach PharmaLabs documentation to batch record

Personnel involved in preparing drug compounds shall be validated for proper technique and understanding of the concepts behind the procedures to be performed. Validation shall be handled under a “pass/fail” grading system. If the individual performing the procedure does not “pass”, then proper retraining and education shall be given and the individual shall be allowed to perform the procedure again until competency is demonstrated.

Outcome of Validation: ☐ Pass ☐ Fail

Re-validation due date: _____

Comments:

_____

_____

Signature: _____ Date: _____
Team Member

Signature: _____ Date: _____
Pharmacy Manager

References:

Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Processes
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)
September 2004
Pharmaceutical CGMPs
Guidance for Industry - Current Good Manufacturing Practice - Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

Media-Fill Test Checklist

Task	Pass/Fail/Completed	Notes
Hand Hygiene		
Garbing and Gowning		
Cleaning and Disinfecting		
Aseptic Manipulation performed properly		
Yield of products appropriate		
Final products devoid of cracks/leaks		
Incubation at 20-25°C for 7 days		
Incubation at 30-35°C for 7 days		
Final products devoid of turbidity or contamination		
Document complete, reviewed and signed		

In Summary

1. Setup	Garbing, cleaning, and preparation in the cleanroom
2. Simulation	Transfer TSB media using aseptic technique
3. Incubation	14 days under proper temperature conditions
4. Evaluation	Check for growth/turbidity — if none, test is “passed”

In Conclusion…

- Media-Fill testing is a simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination
  - Performing personnel aseptic media-fill testing and process verification are critical metrics in any sterile compounding quality system to ensure patient safety
- The number of manipulations of each unit, and the number of units in each sequence should reflect the most complex and prolonged aseptic manipulations likely to be encountered during normal workload production

In Conclusion…

- Detailed documentation is key
  - Regulatory bodies (such as the Centers for Medicare & Medicaid Services [CMS], state boards of pharmacy, state departments of health) and accreditation organizations enforce USP standards and/or include them in their standards
  - If it is not documented, it did not happen
- In case of failure, retraining should consist of reviewing the appropriate SOPs, learning tools, direct mentorship as well as direct observation of all processes

Qualified Personnel and Processes = Patient Safety Assurance

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Questions?

Designated Person
Designing a Media-Fill Test