



Best Practices for Aseptic Media-Fill Testing

UNITED STATES PHARMACOPEIA (USP) GENERAL CHAPTER <797>: PHARMACEUTICAL Compounding – Sterile Preparations recommends minimal requirements for personnel training and evaluation in aseptic manipulation skills. These guidelines apply to all organizations that prepare compounded sterile preparations (CSPs), and are enforceable by the FDA, individual state boards of pharmacy, and accreditation organizations. The aim of USP Chapter <797> is to set consistent compounding standards and increase patient safety.

This article offers steps to comply with the media-fill testing portion of USP Chapter <797>. The chapter is currently undergoing a revision process and the terminology presented will include language from the proposed revisions, which is fairly consistent with the media-fill testing requirements contained in the current version of USP Chapter <797>.



Photo courtesy of Lab Safety Corporation

All employees involved in the preparation of CSPs – including those who check the final product – should participate in media-fill testing.

What is a media-fill test?

Aseptic media-fill testing is used to quantify the aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce a sterile product without microbiological contamination. During this test, a microbiological growth medium, such as soybean-casein digest medium (SCDM), also known as trypticase soy broth (TSB), is substituted for the actual drug product to simulate admixture compounding.¹ After using TSB instead of actual drug product to prepare a simulated CSP, the final container is then incubated and checked for turbidity, which indicates the presence of microbial contaminants.

How often are media-fill tests of personnel required?

Minimally, USP Chapter <797> requires media fill validation initially upon hire, then annually for low- and medium-risk compounding, and twice annually for high-risk compounding. Many organizations choose to perform media-fill testing of employees more often, such as on a quarterly basis, especially if the organization prepares a high daily volume of pharmacy-prepared sterile products.

What pharmacy personnel should prepare media-fill tests?

Other than “personnel who prepare CSPs” USP does not define which employees

at each organization shall prepare media-fills. It is a best standard of practice that all employees involved in the preparation of CSPs participate in the media-fill activity, even pharmacists who generally do not compound sterile preparations, but who check the final product prepared by technicians. Even if a pharmacist or technician only compounds intermittently, they should still be a part of this important step in the quality assurance process.

How is a media-fill test prepared?

USP Chapter <797> provides examples of media-fill test procedures that are considered an adequate representation of each of the three risk levels – low, medium, and high – assigned to CSPs. Organizations may buy the SCDM/TSB media separately or in kits. Media is generally available in sterile vials and bags, and as sterile and non-sterile powder. The exact process below does not have to be followed, but is just an example, presented in USP Chapter <797>. Each organization should review the types of sterile compounding performed and mimic their own procedure as closely as possible. For example, the USP low- and medium-risk media-fill examples do not specifically mention the use of a sterile, lyophilized powder for reconstitution as part

Table 1.	
CSP Risk Level	Example of Media-Fill Test Procedure
Low	Within an ISO Class 5 environment, transfer, with same sterile 10-mL syringe and needle or dispensing pin, three sets of four 5-mL aliquots of sterile SCDM into three separate 30-mL sterile vials.
Medium	Within an ISO Class 5 environment, transfer six 100-mL aliquots of sterile SCDM by gravity through separate tubing sets into separate evacuated sterile containers. Arrange the six containers as three pairs, and use a sterile 10-mL syringe and 18-gauge needle to exchange two 5-mL aliquots of medium from one container to the other in the pair. Then, inject a 5-mL aliquot from each container into a sterile 10-mL clear vial (three total), using a sterile 10-mL syringe and vented needle or pin.
High	Dissolve 3 g of non-sterile commercially available SCDM powder in 100 mL of non-bacteriostatic water to make a 3% non-sterile solution. Withdraw 25 mL of the medium into each of three 30-mL syringes and transfer 5 mL from each syringe into separate sterile 10-mL vials. (These vials are positive controls and will generate exponential microbial growth, for comparison). Next, in an ISO Class 5 environment, affix a 0.2-micron filter and 20-gauge needle to the previously prepared syringes and inject 10 mL from each syringe into three separate 10-mL sterile vials. Repeat for three more vials, affix sterile adhesive seal, and label.

(Information compiled from USP Chapter <797> Proposed Revisions)¹



Compounding

of the process. If your organization reconstitutes antibiotics from lyophilized powder in vials, this should be included in your media-fill validation process. Also, it is suggested that “worst case” conditions (i.e. the end of a busy day to represent possible fatigue, etc.) are mimicked during the media-fill to provide a true evaluation of the types of conditions that would be experienced on a normal workday. In other words, the media-fill tests should mimic the most challenging or stressful conditions that might be encountered during the preparation (and sterilization, when applicable) of CSPs. Additionally, be sure to clear the compounding area of any real patient compounding records, labels, and drug vials, to assure that the TSB media will not be dispensed in error to a patient. See Table 1 for the suggested examples listed in the current proposed revisions to USP Chapter <797>.

How is the prepared final container of media incubated?

The USP Chapter <797> Proposed Revisions indicate that vials should be incubated within a range of 20 to 35°C for 14 days. Failure, or a “positive” test, is indicated by visible turbidity in the medium on or before 14 days. The American Society for Microbiology (ASM) asserts that in their “experience and opinion...a range of 32°C ± 2°C covers a broader spectrum of potential contaminants and pathogens.”² Therefore, a temperature range of 30 to 35°C would likely be acceptable to both the USP and ASM as a range of incubator temperature. It is suggested that a “media-fill results log” be kept, with results documented at days seven and 14 of the incubation process.

What does a turbid or “positive” media test mean?

A positive test could indicate that the compounding employee needs additional training and instruction regarding aseptic technique. Often, simple touch contamination can be the culprit, but a turbid test could also indicate that the controlled cleanroom environment was negatively compromised, possibly due to a malfunctioning blower/motor in a laminar air flow workstation (LAFW) or biological safety cabinet (BSC) or a leak in a hood or cleanroom HEPA-filter. In addition, for high-risk compounding, a positive test could indicate that the integrity of the sterilizing 0.2-micron filter was compromised.

What written policies are needed, and what should be analyzed if the media-fill test is positive?

As part of the aseptic media-fill validation process, written policies and procedures should describe how your organization will meet the USP Chapter <797> requirements and provide employees with a step-by-step process for the media-fill activity. It is suggested that each employee performing media-fill activities have a “mentor” or “buddy” for the activity – someone to verbalize the instructions, step-by-step throughout the activity, and to provide additional observation of aseptic technique. Additionally, the written policy should define the steps to take if a media-fill is positive. Recommended steps include re-training of aseptic technique (with a mentor) and a repeat media-fill test. If tests continue to indicate microbial contamination, further testing of the hoods and cleanroom environment may be necessary. If high-risk compounding is performed during the media-fill, filter integrity may need to be examined as a potential culprit. If environmental air sampling is being performed on a weekly (high-risk) or monthly (low- or medium-risk) basis, review these results to see if any compelling trends are noticed in relation to areas where the positive media-fill activity was performed. All corrective actions and re-testing should be documented as part of the overall quality assurance process.

Trissel, et al, described an unusually high rate of contamination (5.2%) for their annual media-fill validation of 539 employees at the M.D. Anderson Cancer Center.³ As part of their analysis to identify possible causes of the high rate of contamination, they elected to examine their process of wearing non-sterile chemotherapy gloves,



A positive test (center and right) can be caused by touch contamination or a compromised compounding environment, among other possible factors.

Photo courtesy of Q.I. Medical

which were typically disinfected just once with 70% isopropyl alcohol (IPA), after the gloves were initially donned. They tested two additional processes, the results of which were published in April 2007. The first used the same non-sterile chemotherapy gloves, but included steps to disinfect the gloves and fingertips with IPA after every manipulative step of the multi-step media-fill activity. This resulted in a reduction to a 0.96% contamination rate. The second process used sterile gloves with the same frequent disinfection with IPA. This resulted in a contamination rate of 0.34%.⁴ As a result of making a small change in their process – regular disinfection of gloves with IPA – M.D. Anderson significantly reduced their contamination rate in their media-fills. Media-fill activity results and analysis can serve to point out flaws in a process and provide valuable information to further increase patient safety.

What does a “no-turbidity” or “negative” media test mean?

Does it indicate that the organization’s processes are perfect and, therefore, that no further monitoring is necessary? Absolutely not! Periodic media-fills represent a “moment in time” of the whole daily compounding process. Even if all media-fills are negative in an organization, it does not necessarily indicate that no products were ever possibly contaminated. Because the USP’s frequency requirement of media-fill testing is so minimal, organizations will not achieve “statistically significant” results that indicate any particular sterility-assurance level. Unless the microorganisms grow at an exponential rate during the incubation period, a clear media-fill solution could still be observed in the final container, even though that solution may contain some microbial contaminant; smaller quantities are not visible to the human eye. Also, SCDM/TSB do not support the growth of all microorganisms, especially anaerobes.

Conclusion

Along with other quality assurance measures, a robust media-fill program is a necessary step to validate processes of organizations that prepare CSPs. Remember, if the examples given in <797> do not seem to mimic those at your organization, adjust the media-fill process accordingly. There are various commercially available kits that provide the media and instructions needed to minimally comply with the current recommendations. Additionally, most media fill kit vendors will also sell the media separately, so that your organization can obtain the correct quantities needed to con-

 WHERE TO FIND TSB Media and Media Kits	
www.findit.pppmag.com	
Vendor	Reader Service Number
Hardy Diagnostics	77
Lab Safety Corporation/Valiteq	78
Q.I. Medical, Inc.	79

duct a reasonable evaluation of your current compounding practices.

Media-fill testing is just one part of a necessary overall quality assurance program. Alone, it may not provide enough data to fully validate compounding, but it is an important step in the overall pharmacy quality assurance process. One negative media-fill annually does not necessarily "validate" an employee and is not a substitute for regular observation. However, trended results of all employees can provide valuable information regarding processes that may need improvement.

Organizations should check their state's pharmacy regulations to ascertain if the state has any different requirements than those set forth by USP. Additionally, be sure to check the USP website at www.usp.org, for updates and revisions to USP Chapter <797>. ■

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