



# Establishing Your **Sterility Failure Standard Operating Procedure**

**THE ACTIONS THAT SHOULD BE TAKEN IF THERE IS A STERILITY FAILURE IN** your compounding operations are briefly described in USP Chapter <797>: “Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.”

While comprehensive, this statement does not provide a descriptive plan for exactly how to perform an investigation. Do you know what your pharmacy’s procedure is for performing an investigation in the event of a sterility failure in your compounded sterile preparations (CSPs)? Better yet, is your process written down, accurate, and complete? Is your staff empowered and trained to report failures and present ideas for quality improvement?

This article provides a basic outline for a sterility failure standard operating procedure (SOP), including the actions you and your staff should take when performing a comprehensive, well-documented sterility failure investigation. Keep in mind that is essential to train staff in your SOP and provide mechanisms for reporting failures and areas for improvement without making it a finger-pointing exercise. Your SOP may be beautifully written, but it will be useless if it is not followed because your staff is unclear on their role or afraid of being singled out.

The term “sterile” – meaning “free from living microorganisms<sup>1</sup>” – is not absolute. Sterility is measured by the probability of the survival of a microorganism. CSP sterility testing is one way to ensure your compounding staff, practices, environment, materials, and equipment have rendered your CSP sterile, but there are a multitude of variables that must be under a constant state of control during compounding, and your SOP should require you to look into all of them during your investigation. Even if the reason for the failure is obvious, you may be missing opportunities to improve or correct other areas of deficiency if you stop your investigation with the first discovery of a possible root cause.

Sterility failure investigations should be designed to test and challenge all of the pharmacy’s compounding quality controls. Your procedure should include a uniform reporting mechanism for documenting the results of your investigation, such as a sterility investigation report form in the appendix of your SOP. It is a good idea to use a sequential numbering system and to assign a number to each inspection report form at the time an investigation is initiated. A completed investigation report becomes part of your compounding record, and you should keep the report for as long as your state regulations require you to retain compounding records.

## The Basic Elements of the SOP

Following are the elements that should be included in your SOP.

**Purpose:** One or two sentences stating the SOP’s purpose

**Scope:** Describe what the SOP applies – and does not apply – to. Departments, equipment, systems, and so on should be included.

**Definitions:** Any necessary definitions of terms and acronyms should be included to assure the staff’s uniform understanding of them.

**Responsibilities:** Everyone must understand their role in this process. Describe who, by position or title rather than name, should be responsible for learning and executing the sterility investigation.

**Procedure:** Anyone reading the SOP should be able to follow the concise step-by-step sequence of events to complete the procedure from beginning to end. This portion is written for use as a training tool and should accurately and sequentially list the activities performed regularly and consistently every time the procedure is followed.

**SOP Revision History:** List any changes made to the SOP, indicating the section that was changed and the reason for the change, as well as the author and date. Previous changes should not be deleted from your table.

**References:** Any SOPs, forms, or manuals used to write the SOP should be included in this section. References should include the name and edition of the document and where it can be found.

**Appendices:** These tables, charts, lists, etc. will help the reader to fully comprehend and follow the procedure.

## Capturing Your Procedure

The procedure section of your SOP should describe all of the steps to take during an investigation. To identify all of these steps, visually map the process. Involve your staff at this point to gain their perspective on what is and should be done. Your procedure should include any immediate actions and notifications to management and staff. Even more importantly, it should address common cause-and-effect variables that may have contributed to the failure. Subheadings in this section may describe how you investigate variables such as people, environment, equipment, materials, and methods<sup>2</sup>. Once you have your process mapped around these items, be sure it is clear who performs each investigational task.

## Immediate Steps Following a Sterility Failure

The first step should be an immediate quarantine of the CSPs involved. Next, if it is an autoclaved CSP, consider quarantining the equipment until the investigation is completed, or at least until the equipment has been checked and revalidated, if necessary. Finally, use your logs to identify other CSP lots that may also be affected. For example, check the CSPs made in the same timeframe, with the same equipment, or with the same formulas related to more than one sterility failure over time. If your investigation results show a potential adverse effect to multiple lots of CSPs – a failing autoclave, for example – you may decide to perform a recall of all affected lots, even if no positive biological indicators were found in those lots.

## The Investigation

Ensuring sterility involves the oversight and control of multiple factors: people, environment, equipment, materials, and measures/metrics. These parameters should be constantly measured and recorded to verify that your processes are under control, and each of them needs to be addressed in depth in a failure investigation. A sterility failure may indicate a problem in your process and you should, from a quality-improvement perspective, take a hard look at all components of your process and preparation.

Once your immediate quarantine actions have been taken, start your investigation by tracking the finished preparation back to its raw materials – commonly called “backward tracing.” Compile copies of all of the documentation associated

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with the CSP (formula worksheets, room logs, environmental monitoring data, equipment logs, etc.), and record all of your results in the investigation form and keep the copies with the report. In the event of a regulatory investigation, this documentation is essential to show inspectors that a thorough investigation has been performed.

**Staff:** Operators have the highest potential to introduce microbial contamination to a CSP. Check if the operator who made the CSP is new, was sick the day the CSP was made, or if he or she may have compounded other CSPs that resulted in a sterility failure. Ask the operator if he or she remembers any details associated with this CSP, such as equipment, workload, or any events of the day that may have caused a shift in any areas of the compounding process.

Watch your staff during compounding. Are their activities in line with your compounding SOP? Does staff need to be retrained, or is the SOP incorrect? Remember, operators are not only the number-one source of potential contamination, but they can also introduce the most variability into a process, affecting the quality of your CSPs<sup>3</sup>.

**Environment:** For terminally sterilized (autoclaved) CSPs, see if there is an upward trend of biological indicator (BI) failures – a sign that your autoclave may be operating out of specification. Check the Certificate of Analysis on the lot of BIs used to confirm that they are within their expiration date and that they have been stored under proper conditions. Ask the BI manufacturer if they received any complaints on that lot of indicators.

For CSPs that are sterilized by filtration, review your environmental monitoring data for any trends. Room temperature and humidity logs, alongside your surface and air monitoring results, should be reviewed for upward trends. Were any of these results out of specification during the time your CSP was made?

An increase in air and surface colony-forming units may indicate a problem. Your cleaning agents and schedules should eradicate the kinds of microbes identified as potential contaminants in your cleanrooms. Likewise, your staff should be cleaning according to procedure, with documented training and observation. Recent cleanroom



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construction can also release contaminants into your environment.

Sterility test results from a testing laboratory showing multiple failures may indicate a problem on the laboratory's end. Multiple false positives could be a result of a deviation from testing protocols, a new employee, etc. If such trends appear, ask questions.

**Equipment:** Was the equipment used to prepare the CSP in good working order and verified as such by the operator? Check if the equipment used was serviced recently. If your equipment is under a maintenance contract, record the dates of service. Be sure your staff is sanitizing equipment correctly.

**Materials:** Have you recently changed your packaging or source of raw materials? For example, did you change suppliers for your vials, stoppers, or testing media? Has your vendor had problems with or issued any recalls for the sterility of their packaging, filters, media, etc.? For refrigerated materials, check your temperature logs for excursions.

**Methods:** Ask your operators if there have been any changes in the compounding process. Process changes can have a direct impact on the finished CSP. Have changes been reflected in the compounding instructions? If no, why not? Has this new process been tested to ensure it works and has a pharmacist approved it? Is staff aware that making changes to a verified process can cause problems from both a quality and regulatory perspective?

#### Documenting Observations and Possible Causes for Failures

Complete chronology and documentation of your findings, including the possible root cause and corrective actions will be helpful, in the event of an audit or if the problem arises again. Any discrepancies should be addressed, and a corrective action should be proposed, assigned, and completed by the responsible person. All of these steps need to be documented in your investigation report. More importantly, the report needs to show evidence that the corrective or preventative actions identified and assigned were completed, who completed them, and when they were completed.

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## Reviewing Observations

Reports should be completed and closed in a reasonable timeframe and filed in a central location. Management should review the reports and provide any additional input as necessary. Keeping management informed is essential to ensuring awareness and resolution of issues. The investigator or quality reviewer should document the closure of the investigation and provide a brief summary of the results and action items.

Consider including a “review” section in your SOP to demonstrate that reports are not just completed and filed away. A qualified staff member or a quality review team should review the reports, thus directly tying your investigation process into your continuous quality improvement program.

## Conclusion

In your pharmacy, a sterility failure should be the catalyst for a “rapid and systematic investigation” – one that is performed consistently, as documented in your sterility failure investigation SOP. Good recordkeeping, in addition to a uniform process for investigations, will provide you the opportunity to confirm and/or deny the source of a failure and identify areas for improvement in any area of your process. ■

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## References

1. Block SS. Definition of Terms. In: Block SS, Ed. *Disinfection, Sterilization, and Preservation*, 5th ed. Lipincott, Williams & Wilkins, 2001: 25.
2. Tague NR. *The Quality Toolbox*, Second Edition, ASQ Quality Press, 2004: 247-249.
3. PDA Technical Report No. 13 – Fundamentals of an Environmental Monitoring Program.

## WHERE TO FIND Sterility Testing Equipment:

Vendor	Reader Service Number
Lab Safety Corporation	43
Microtest	44
Millipore	45
Q.I. Medical Inc.	46