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Board of Registration in Pharmacy

Policy 2025-01: Rapid Microbial Methods (Rapid Sterility Testing)

The Massachusetts Board of Registration in Pharmacy ("Board") adopts this policy regarding the use of Rapid Microbial Methods ("RMMs") as an alternative for sterility release testing of compounded sterile preparations ("CSP") by Massachusetts-licensed sterile compounding pharmacies.

The purpose of this policy is to safeguard the public by outlining requirements for the use of such technologies. It is the position of the Board [Draft 247 CMR 17.17 (2)] that a pharmacy may not dispense a CSP that requires sterility testing unless and until it first receives negative sterility test results.

In accordance with USP <797>, sterility testing must be performed according to USP <71> or a validated alternative method that is noninferior to USP <71>. As a reminder, state law requires sterile compounding pharmacies to "adhere to the most current standards established by USP, all chapters, when engaging in any form of sterile compounding."

I. General Considerations

A. Has the RMM method been validated and demonstrated to be suitable for its intended use in accordance with USP chapters *Validation of Alternative Microbiological Methods* <1223> and *Validation of Compendial Procedures* <1225>?
B. Does the RMM get comparable results (non-inferior) to the standard compendial test (USP <71>)? What is the limit of detection of microorganisms with the specific technology (i.e., does the RMM detect low levels of microorganisms)?
   For growth-based RMMs, does the RMM detect microorganisms in a short incubation period? For example, slow growing microorganisms or a lag in growth due to any antimicrobial activity of the drug formulation (i.e., active drug and / or excipients).

C. Do the microorganisms used in method suitability challenge testing resemble microorganisms typically found in the specific pharmacy's sterile compounding environment and / or sterility test failures (i.e., those beyond USP challenge microorganisms). Does the challenge testing include slow growing microorganisms (e.g., penicillium, etc.)? Would the laboratory be able to incorporate additional microorganisms into the testing?
D. What are the limitations of the selected RMM?
    1. Does the method identify all microbes? For example, some O2 methods may not be able to identify anaerobic microbes.
    2. Does it enable the pharmacy to recover and identify microorganisms to conduct full investigations for failed sterility tests in accordance with USP <797>? For example, is the RMM destructive to the test sample? Does it require the pharmacy to retain additional samples to aid in such investigations?
    3. If applicable, does the RMM method require different types of growth media and incubation procedures (e.g., times, temperatures, etc.)?

II. Pharmacy Responsibilities

Pharmacies considering the use of RMM's must exercise due diligence by:

A. verifying that the specific alternative method / technology has been fully validated (i.e., method validation) to demonstrate that it is equivalent or superior to the compendial method outlined in USP <71>.
B. conducting a risk assessment to ensure that there is built-in quality. For example, is the specific method destructive to the sample? If so, how will sterility failures be investigated? Does it require the pharmacy to retain additional samples to aid in such investigations?
C. ensuring that method suitability challenge testing for CSPs is performed. The method suitability challenge testing must demonstrate recovery of low levels of the microorganisms (bacteria, yeast, and mold) specified in USP <71>.
    1. verify that the method suitability challenge testing has been conducted <u>for each</u> CSP formulation to validate that it does not inhibit or interfere (e.g., false positives, false negatives, etc.) with the rapid sterility test and provides the same result as the standard (USP <71>).
    2. verify that the method suitability challenge testing was conducted with the pharmacy's sample (e.g., specific concentration, same API Chemical Abstracts Service (CAS) Number, etc.).
    3. consult with the laboratory to determine if challenge testing should include additional microorganisms that have been identified in the pharmacy's environmental monitoring, personnel monitoring, and failed sterility testing.

4. Method suitability must be repeated for CSP formulation changes or any other pertinent product composition changes.
5. utilizing a properly credentialed / qualified laboratory capable of conducting rapid sterility testing with a specific RMM(s) and appropriate method suitability challenge testing. Conduct an audit to:
    a. evaluate credentials and training of microbiology analysts / professionals.
    b. evaluate the laboratory's policies and procedures for such testing.
    c. assess the facility by conducting an in-person or virtual tour of the facility, if possible.

III. Documentation Requirements

Pharmacies must maintain the following documentation obtained from the qualified laboratory conducting RMM testing and have it readily available for the Board upon inspection or request.

A. The primary validation package received from the supplier of the equipment / technology proving / verifying that the RMM being utilized is non-inferior to USP <71>.
B. Reports / statements from the qualified laboratory of completed method suitability challenge testing for each CSP formulation. Reports / statements must include at least the following:
    1. description of CSP formulation (e.g., drug, concentration, volume, etc.)
    2. specific organisms used in challenge testing.
    3. type(s) of media used, if applicable.
    4. incubation details (temperature / duration), if applicable.
    5. documented results (pass or fail per USP <71>).
    6. signature of a microbiologist.
C. Once the method suitability challenge test results are received, the Manager of Record or Designated Pharmacist-in-Charge must review, sign, and date the document.

Please direct any questions to: **Pharmacy.Admin@mass.gov**

References

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USP General Chapter <71> Sterility Testing
USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations
USP General Chapter <1071> Rapid Microbial Tests for Release of Sterile Short-Life Products: A Risk-Based Approach
USP General Chapter <1223> Validation of Alternative Microbiological Methods
USP General Chapter <1225> Validation of Compendial Procedures
U.S. Pharmacopeial Convention, Rockville, Maryland
https://www.uspnf.com/

USP Pharmacopeial Forum 43(5): Sep.-Oct. 2017. Stimuli to the Revision Process. The Development of Compendial Rapid Sterility Tests. pp. 595-610.

https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/pf-legacy-pdf/pf-2017_vol-43.pdf

USP Pharmacopeial Forum 44(5): Sep.-Oct. 2018. General Information Chapter <1071> Rapid Sterility Testing of Short-Life Products: A Risk-Based Approach. pp. 3190-3203. https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/pf-legacy-pdf/pf-2018_vol-44.pdf