Disclaimer

• I am making this presentation as an independent agent
• I am not making this presentation as a representative of USP, PDA, PMF, SCA or any other organization with which I am currently associated.
• The views expressed in this presentation are offered as mine alone.
Overview of Presentation

- Who Cares?
- What are the compendial Sterility Tests?
- Product Requirements
- Method Suitability
- Alternate Methods

Table 1. Issues in Compounding Pharmacies Identified by FDA 483 Observations*

<table>
<thead>
<tr>
<th>Pharmacy Name</th>
<th>SDM to Prevent Microbial Contamination Non-compliance or Not Followed</th>
<th>Inadequate/Improper ER</th>
<th>Stability Program</th>
<th>Inadequate Handling/Storage</th>
<th>Batch Release</th>
<th>Validation of Bioburden/Control</th>
<th>Lab Procedures/Testing/Control/Lab Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Pharmacy Consulting</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>1, 6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced Pharmacy Consulting</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>1, 7</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA Central Pharmacy (Closed)</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1, 6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA Manufacturing</td>
<td>4</td>
<td>0</td>
<td>6</td>
<td>1, 7</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA Northeast</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>1, 6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Lab</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1, 6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacy</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>1, 6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corporate Drug Test</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>1, 6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA


http://www.americanpharmaceuticalreview.com/Featured-Articles/135985-GMP-and-Compounding-Pharmacies/
Frequent 483 Citations - Initial

Frequent 483 Citations - Current
## Frequency of Issue Cited

<table>
<thead>
<tr>
<th>Topic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate/ Improper EM</td>
<td>81.1%</td>
</tr>
<tr>
<td>Validation of Sterilization - Media Fills</td>
<td>79.7%</td>
</tr>
<tr>
<td>Stability Program</td>
<td>78.4%</td>
</tr>
<tr>
<td>Lab Procedures: Testing/ Contract Lab Control</td>
<td>74.3%</td>
</tr>
<tr>
<td>SOPs to Prevent Microbial Contamination Non-existent or Not Followed</td>
<td>73.0%</td>
</tr>
<tr>
<td>Inadequate Gowning</td>
<td>70.3%</td>
</tr>
<tr>
<td>Batch Release</td>
<td>60.8%</td>
</tr>
<tr>
<td>Inadequate Cleaning/ Disinfection</td>
<td>60.8%</td>
</tr>
<tr>
<td>Control of Equipment</td>
<td>60.8%</td>
</tr>
<tr>
<td>Inadequate Facility / Smoke Studies</td>
<td>54.1%</td>
</tr>
<tr>
<td>Investigations</td>
<td>50.0%</td>
</tr>
<tr>
<td>Control of Pyrogenic Contamination</td>
<td>47.3%</td>
</tr>
<tr>
<td>QAU Not Effective/ Production SOPs not followed/effective</td>
<td>43.2%</td>
</tr>
<tr>
<td>Separation of Clean and Dirty Operations/Storage of Materials</td>
<td>31.1%</td>
</tr>
<tr>
<td>Inadequate Raw Material Control</td>
<td>27.0%</td>
</tr>
<tr>
<td>Container Preparation</td>
<td>18.9%</td>
</tr>
<tr>
<td>SOP/Control of Production</td>
<td>17.6%</td>
</tr>
<tr>
<td>Safeguard Against Penicillin/Cephalosporine Cross Contamination</td>
<td>14.9%</td>
</tr>
<tr>
<td>Labelling Issues</td>
<td>13.5%</td>
</tr>
<tr>
<td>Records not Available</td>
<td>12.2%</td>
</tr>
<tr>
<td>Personnel not Trained/ Inadequate</td>
<td>5.4%</td>
</tr>
<tr>
<td>Obvious Product Contamination (Micro/Particulate)</td>
<td>4.1%</td>
</tr>
<tr>
<td>Change Control</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

### 483 issued 12/20/13

**Observation 2**

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically, your firm does not test and review results for sterility of drug products prior to releasing products for distribution. Also, your firm does not perform test on all batches.

On December 13th, 2013, we reviewed your firm's written procedure for conducting sterility tests on sterilized drug products (SOP #9.120; ver 7.0, eff 2/1/2013) which reads in part that randomly selected formulas will be tested for sterility. Your pharmacist stated that batches greater than 100 units in size are sent to a third party lab for sterility testing and the product is not currently released until sterility results are received from the lab. However, your firm does not always wait to release product until sterility testing is complete, for example:
483 Issued 4/17/13

OBSERVATION 7

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically, your firm produced and distributed about 101 lots of injectable drug products for the period between 3/12-3/13. The sterility testing performed by your contract laboratory consists of a "Plate Contamination" test or a "Anastomosis" test. However, your firm provided no data to demonstrate that either method is equivalent to or better than the USP 71 sterility method.

Sterility testing, as defined under USP 71, was conducted for only 2 lots during the designated time period.

483 Issued 1/9/14

OBSERVATION 3

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically,

Finished product Sterility testing is not always conducted for aseptically processed drug products. For example, Calcium Gluconate 10% Injectable vials, Lot# 117433@13 produced on 11/07/13 was not sampled for USP sterility testing. In addition, an endotoxin analysis was not performed.
Overview of Presentation

• Who Cares?
• What are the compendial Sterility Tests?
• Product Requirements
• Method Suitability
• Alternate Methods

Sterility Testing

• Two separate tests
  • Membrane Filtration
  • Direct Transfer
• 20 Units, 2 media & temperatures
• Requires Growth
  • Incubation period - 14 days
Membrane Filtration

- Filter required amount of product through two filters
- Neutralize/Rinse
  - 3 100 mL volumes suggested
  - Formulations for dilution fluids suggested
- One filter into Soybean Casein Digest Broth (SCDB or TSB) – incubate at 20-25°C for 14 days
- One filter into Fluid Thioglycollate Medium (FTM) – incubate at 30-35°C for 14 days

Direct Inoculation

- Place required amount of product into sufficient recovery medium (with neutralizers?)
  - Soybean Casein Digest Broth (SCDB or TSB) – incubate at 20-25°C for 14 days
  - Fluid Thioglycollate Medium (FTM) – incubate at 30-35°C for 14 days
## Product Requirements – Minimum Quantity per Unit for Each Medium

### Liquids

<table>
<thead>
<tr>
<th>Minimum Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mL</td>
</tr>
<tr>
<td>1-40 mL</td>
</tr>
<tr>
<td>&gt;40 - &lt;100 mL</td>
</tr>
<tr>
<td>&gt;100 mL</td>
</tr>
<tr>
<td>Antibiotic Liquids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimum Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The whole contents of each container</td>
</tr>
<tr>
<td>Half the contents of each container, but not less than 1 mL</td>
</tr>
<tr>
<td>20 mL per container</td>
</tr>
<tr>
<td>10% of the contents of the container, but not less than 20 mL</td>
</tr>
<tr>
<td>1 mL</td>
</tr>
</tbody>
</table>

### Solids

<table>
<thead>
<tr>
<th>Minimum Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 mg</td>
</tr>
<tr>
<td>50 - &lt;300 mg</td>
</tr>
<tr>
<td>300 mg – 5 g</td>
</tr>
<tr>
<td>&gt;5 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimum Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The whole contents of each container</td>
</tr>
<tr>
<td>Half the contents of each container, but not less than 50 mg</td>
</tr>
<tr>
<td>150 mg per container</td>
</tr>
<tr>
<td>500 mg per container</td>
</tr>
</tbody>
</table>

*Insoluble preparations, creams, and ointments to be suspended or emulsified - Use the contents of each container to provide not less than 200 mg*
### Number of Units to be Tested

<table>
<thead>
<tr>
<th>Number of Units to be Tested</th>
<th>Minimum Number of Units to be Tested for Each Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral preparations</strong></td>
<td>- Not more than 100 containers: 10% or 4 containers, whichever is greater&lt;br&gt;- More than 100 but not more than 500 containers: 10 containers&lt;br&gt;- More than 500 containers: 2% or 20 containers, whichever is less&lt;br&gt;- For large-volume parenterals: 2% or 10 containers, whichever is less</td>
</tr>
<tr>
<td><strong>Antibiotic solids</strong></td>
<td>- Pharmacy bulk packages (&lt; 3 kg): 20 containers&lt;br&gt;- Pharmacy bulk packages (≥ 3 kg): 6 containers&lt;br&gt;- Bulks and blends: See Bulk solid products.</td>
</tr>
<tr>
<td><strong>Ophthalmic and other noninjectable preparations</strong></td>
<td>- Not more than 200 containers: 5% or 2 containers, whichever is the greater&lt;br&gt;- More than 200 containers: 10 containers&lt;br&gt;- If the product is presented in the form of single-dose containers, apply the scheme shown above for preparations for parenteral use.</td>
</tr>
<tr>
<td><strong>Cutting and other surgical sutures for veterinary use</strong></td>
<td>- Not more than 100 articles: 2% or 5 packages, whichever is the greater, up to a maximum total of 10 packages&lt;br&gt;- More than 100, but not more than 500 articles: 10% or 4 articles, whichever is greater&lt;br&gt;- More than 500 articles: 2% or 20 articles, whichever is less.</td>
</tr>
<tr>
<td><strong>Bulk solid products</strong></td>
<td>- Up to 4 containers: Each container&lt;br&gt;- More than 4 containers, but not more than 50 containers: 2% or 4 containers, whichever is greater&lt;br&gt;- More than 50 containers: 2% or 10 containers, whichever is greater</td>
</tr>
</tbody>
</table>

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### Example 1 - 84 units of 10 mL

- **10 mL is between 1 and 40 mL** – Table 2 tells us to use ½ volume or 5 mL per unit
- **84 units is less than 100** – Table 3 tells us to use the greater of 4 units or 10% of the batch = 8 units per medium
- **We therefore must test at least 5 mL from each of 8 units for each medium**
Example 2 – 6 units of 1.5 mL

- 1.5 ml is between 1 and 40 mL – Table 2 tells us to use ½ volume but not less than 1 mL – therefore we test 1 mL mL per unit
- 6 units is less than 100 – Table 3 tells us to use the greater of 4 units or 10% of the batch = 4 units per medium
- We therefore must test at least 1 mL from each of 4 units for each medium.

483 Issued to Testing Lab #1

1. Your firm states on the Microbiology Report that is issued to a client after sterility and/or fungal testing that the Test Method employed was USP <71>. However, your firm is not fully following all parts of USP <71> when performing sterility and/or fungal testing of human drug products. For example,

b. USP <71> specifies the number of articles to be tested. While you provide reference to USP <71> for sample sizes, you do not ensure that your clients are submitting the required number of articles for testing. Most clients usually submit only 1(4) for sterility testing, including
483 Issued to Testing Lab #2

OBSERVATION 1

Test procedures relative to appropriate laboratory testing for sterility are not followed. Specifically,

A. Certificates of Analysis (CoA’s) your firm issues to customers for sterility testing cite USP <71> as the method used for testing. This was observed during the inspection of your laboratory for sterility testing. However, your firm is not following USP<71> when testing these products for sterility assurance. USP <71> specifies the number of articles to be tested based on the overall batch size of the drug product. USP <71> also specifies the number of articles to be tested when the batch size is unknown. Your Quality Assurance Lead stated your firm does not require batch size information from clients for samples tested per USP <71>, nor is this information routinely shared with your firm.

Your firm recommends to customers to follow USP<71> for sampling products for sterility testing; however there are no documents, correspondences, or procedures in place to guarantee your customers routinely submit the required number of articles for sterility testing, whether or not this is for initial sample submission or customer-requested re-test.

483 Issued to Testing Lab #2
(cont)

B. In addition, your firm did not assure the required number of articles specified per USP <71> were submitted for testing and re-testing of drug product glutathione/vitamin C/DMSO 1.25%/1.25%/6.25%, lot #2012, on 8/15/2012 and 8/20/2012, respectively.

C. Your written procedure MIC-SOP-0016 reads “The client must specify if re-testing can occur from the original sample or if they are sending in a new sample from the same lot. Re-testing can only be justified in the event of a proven lab OOS. New results cannot replace previous OOS results.” The procedure does not define “proven lab OOS,” nor does it describe the criteria for invalidating an OOS test result not shown to be a “proven lab OOS.”
483 Issued to Lab #3

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, and test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity.

Specifically,

B) Your firm does not conduct growth promotion on the [redacted] used in their membrane filtration and direct inoculation sterility tests for drug product as required in the USP <71> Sterility test.

C) There is no suitability testing performed on drug product samples prior or concurrently during membrane filtration sterility testing as required in the United States Pharmacopeia Chapter <71> Sterility Tests.

D) Your firm does not indicate the number of samples received or required for sterility testing. USP <71> specifies the number of articles to be tested. While you provide reference to USP <71> for sample sizes, you do not ensure that your clients are submitting the required number of articles for testing.

E) Your firm has not validated your "plate contamination method" to determine whether it is suitable for its intended use by the customer as a sterility test method.

F) Your firm does not conduct growth promotion on the [redacted] plates used in testing drug product samples for microbial contamination via the [redacted] Microbial Plating method.

483 Issued to Lab #3 (cont)

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, and test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity.

Specifically,

H) Certificates of Analyses of commercially purchased media used to test drug products for sterility tests [redacted] and Microbial plate contamination test using [redacted] are not maintained.
Overview of Presentation

• Who Cares?
• What are the compendial Sterility Tests?
• Product Requirements
• Method Suitability
• Alternate Methods

Method Suitability Test

Can we neutralize any antimicrobial properties of the medication?

Use specified challenge organisms
Use specified total amounts of products
Method Suitability Test for Each Challenge Organism

- Filter maximal amount of medication to be tested
- Filter 2 volumes (100 mL?) of diluting fluid
- Add third volume, inoculate with <100 CFU challenge organism
- Filter
- Show microbial growth from filter in relevant medium at relevant temperature in 5 days

Method Suitability Test

6 challenge organisms
- FTM
  - C. sporogenes
  - P. aeruginosa
  - S. aureus
- SCDB
  - A. brasilensis
  - B. subtilis
  - C. albicans

Table 1. Strains of the Test Microorganisms Suitable for Use in the Growth Promotion Test and the "Method Suitability" Test

<table>
<thead>
<tr>
<th>Organism</th>
<th>ATCC</th>
<th>CIP</th>
<th>NCTC</th>
<th>NCIMB</th>
<th>NBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus*</td>
<td>ATCC 6538</td>
<td>CIP 4.83</td>
<td>NCTC 10788</td>
<td>NCIMB 9518, NBR 13276</td>
<td></td>
</tr>
<tr>
<td>B. subtilis</td>
<td>ATCC 6633</td>
<td>CIP 52.62</td>
<td>NCTC 8054</td>
<td>NCIMB 3134</td>
<td></td>
</tr>
<tr>
<td>B. subtilis</td>
<td>ATCC 9027</td>
<td>CIP 82.118</td>
<td>NCIMB 8626</td>
<td>NBR 13275</td>
<td></td>
</tr>
<tr>
<td>Anaerobic bacterium</td>
<td>ATCC 19404</td>
<td>CIP 79.3</td>
<td>NCTC 532</td>
<td>ATCC 11437, NBR 14293</td>
<td></td>
</tr>
<tr>
<td>A. brasilensis</td>
<td>ATCC 10231</td>
<td>IP 48.72</td>
<td>NCPF 3179</td>
<td>NBR 1594</td>
<td></td>
</tr>
<tr>
<td>B. subtilis</td>
<td>ATCC 14404</td>
<td>IP 1431.83</td>
<td>JMI 149007</td>
<td>NBR 9455</td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>ATCC 15230</td>
<td>IP 48.72</td>
<td>NCPF 3179</td>
<td>NBR 1594</td>
<td></td>
</tr>
</tbody>
</table>

* **An alternative microorganism is Kocuria rhizophila (Micrococcus luteus, ATCC 9341).**
* **An alternative to Clostridium sporogenes, when a nonspore-forming microorganism is desired, is Bacteroides vulgatus (ATCC 8452).**
Method Suitability – Examples

- Example 1 - 84 units of 10 mL
  - 5 mL from 8 units = 40 mL for each organism; there are 6
  - $6 \times 40 \text{ mL} = 240 \text{ mL}$ total for Method Suitability

- Example 2 – 6 units of 1.5 mL
  - 1 mL from 4 units = 4 mL for each organism
  - $6 \times 4 \text{ mL} = 24 \text{ mL}$ total for Method Suitability

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483 Issued to Testing Lab #1

1. Your firm states on the Microbiology Report that is issued to a client after sterility and/or fungal testing that the Test Method employed was USP <71>. However, your firm is not fully following all parts of USP <71> when performing sterility and/or fungal testing of human drug products. For example,

   a. USP <71> requires a Method Suitability Test be performed for all new products tested. Your firm does not have documentation to show that Method Suitability Testing has been performed for all drug products submitted for sterility testing by Ameridose, LLC and New England Compounding Center (NECC), both located in Massachusetts. For those drug products submitted by New England Compounding Center (NECC), you have some documentation of bacteriostasis/fungistasis testing performed in 2006 & 2008 on a limited number of drug products, however there is no source documentation showing how the tests were performed, lot numbers of organisms or media used, and who performed the testing.
483 Issued to Lab #2

OBSERVATION 1

Test procedures relative to appropriate laboratory testing for sterility are not followed. Specifically,

D. Also, your firm has not performed validation of sterility testing for currently-tested drug products containing any of __ different active ingredients, for clients including [(b)(4)]

483 Issued to Lab #3

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, and test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity. Specifically,

G) Finished product samples tested for microbial contamination using the [(b)(4)] Microbial Plating Method were not tested for suitability to neutralize preservative interference and/or inhibition if present in finished product.
483 Issued to Lab #4

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

There is no verification of any methods reported to be USP and/or validation of any internal methods for any drugs tested, this is evidenced by:

1) Sterility Testing and 14-Day Sterility Testing
   a. Your firm has not performed any verification of any methods reported to be USP and/or validation of any internal methods, this includes Accelerated Sterility Testing which has been in place since 2004.
   i. No validation studies have been conducted for the accelerated sterility testing, including studies that demonstrate equivalency to USP <71> Sterility testing. As of this date, approximately 25% of all sterility testing (according to analysts, approximately 30% sterility samples are received/tested daily) is done using the accelerated sterility testing method. Your firm's Sterility Testing SOP (MICRO-SOP-004) has no provisions for the microbial growth media to be challenged with Growth Promotion Testing. The reliability of this sterility test has not been shown to be validated with the Bacteriostatic and Fungistatic test; these tests have not been conducted. Additionally,
      1. No validation studies have been conducted on the Flow cytometer used for Accelerated Sterility testing.

483 Issued to Lab #4 (cont)

b. Your firm is without any verification of any methods reported to be USP and/or validation of any internal methods, this includes 14-day USP <71> Sterility Testing.
   i. No Growth Promotion Test and Bacteriostatic and Fungistatic Tests have been conducted in accordance with USP <71> for any drug tested at any time. Sterility testing consists of that approximately 25% of all sterility testing is done using the traditional 14-day sterility testing. Your firm's Sterility Testing SOP (MICRO-SOP-009) provides no provisions for Growth Promotion Test and the Bacteriostatic and Fungistatic Test.
   1. No verification of microbial growth, such as gram staining, is performed on positive ( turbid) results from plates, in order to verify growth and to determine if microorganisms are present. General media plates are used for sub-culturing positive ( turbid) results and they are being incubated aerobically. If growth is observed on the primary plates, identification(s) are performed.
   2. No definitive read dates for the sterility tests are recorded on laboratory worksheets indicating when the final read of each individual sample takes place. According to a sterility analyst, there is a final date that represents when all samples on one worksheet were finalized. This includes any culturing due to positive results. In some instances, 14-day Sterility Testing worksheets indicate that the incubation period was less than the required 14-day period required by USP <71>. It cannot be verified that samples were run for the specified 14-day period if a final read date is not recorded for every sample.
Review of Presentation

• Who Cares?
• What are the compendial Sterility Tests?
• Product Requirements
• Method Suitability
• Alternate Methods

Alternate Sterility Tests

• Clearly allowed by USP
• Must be demonstrated as “equivalent or better” than USP <71>
  • Specificity
  The test’s ability to detect a range of microorganisms in the sample
  • Limit of Detection
  The lowest number of microorganisms that can be detected by the test
  • Ruggedness
  The performance of the test under a variety of “normal” test conditions
  • Robustness
  The capacity of the test to give consistent results under different method parameters
Compounding Pharmacies and the Sterility Test

483 Issued to Lab #3

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, and test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity.

Specifically,

A) There is no validation performed on the instrument to determine its suitability for use as a sterility test for product that they test.

483 Issued to Lab #4

OBSERVATION 1

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

There is no verification of any methods reported to be USP and/or validation of any internal methods for any drugs tested, this is evidenced by:

1) Sterility

a. Your firm has not performed any verification of any methods reported to be USP and/or validation of any internal methods, this includes Accelerated Sterility Testing which has been in place since 2012.

1. No validation studies have been conducted for the accelerated sterility testing, including studies that demonstrate equivalency to USP <71>. Sterility analysts indicated that approximately 25% of all sterility testing (according to analysts, approximately 200 sterility samples are received/tested daily) is done using the accelerated sterility testing method. Your firm's Accelerated Sterility Testing SOP (MICRO-SOP-034) has no provisions for the microbial growth media to be challenged with Growth Promotion Testing. The reliability of this sterility test has not been shown to be validated with the Bacteriostatic and Fungistasis test; these tests have not been conducted. Additionally,

1. No validation studies have been conducted on the Flow cytometer used for Accelerated Sterility testing.
2. No verification of microbial growth, such as gram staining, is being performed on [certain tubes] that are resulted as a “fail” by the [preliminary test]. As part of your process when a “fail” is resulted, a subculture is performed from the broth to a [plate]. The [plate] is incubated for [time] under aerobic conditions. Identification is performed if any growth is observed on the [plate]. Therefore, a verification of microbial growth, such as a gram stain, is needed in order to determine what the expected growth should be on the [plates].

3. [a procedure] which is used to culture anaerobic microorganisms, is being used as part of [another procedure] to allow for the growth of anaerobic microorganisms.

4. You are not following procedure (MICRO-SOP-4024). According to your procedure, the accelerated sterility testing is to be performed using [certain broths]. When broths are analyzed using the [procedure], there are inconsistencies with the number of broths analyzed. In numerous instances, only one broth tube (or [tubes]) was analyzed instead of [two].
ii. In the event that an initial sterility test result is found to be a “fail”, subculture of broth tubes and a subculture using plates is performed. When no growth is observed on the subculture plates, a passing result is reported to the customer. For example, sample: Bevacizumab 25mg/mL, expiry 11/5/2013, failed sterility test on 8/14/2013, and was subcultured on 8/16/2013. No growth was found on subculture, and a passing sterility result was reported to the customer on 8/20/2013. There are 33 examples using this same follow-up method for finished products which are still within expiry, between the time period of 5/1/2013 through 8/20/2013. The above follow-up method has not been validated, including demonstration of equivalency to the methods described within USP <71> as required. In addition, your firm does not investigate all sterility failures to determine whether results can be invalidated.

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Your accelerated testing procedure (MICRO-SOP-024) is inadequate because fastidious growing microorganisms, anaerobes and molds may not be recovered since broth is only incubated for 48 hours. Additionally, plates are being used for sub-culturing and have not been shown to support growth of a wide-range of microorganisms. These plates are only being incubated aerobically for 7 days. Subsequently, since no verification of microbial growth (such as gram staining), is performed on broths, there is no way to determine if microorganisms should have been recovered.
Review of Presentation

- Who Cares?
- What are the compendial Sterility Tests?
- Product Requirements
- Method Suitability
- Alternate Methods

Further Reading

BEFORE WE HAVE THE QUESTIONS

Thank you to our sponsor for this webinar -

Considerations for Choosing a Sterility Testing Vendor

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5 Important Considerations
Choosing a Sterility Testing Vendor

1) Look for high quality products and standards
   • Leads to consistent and accurate results, reliability
   • Documentation (Certificate of Quality or Analysis)
   • Minimizes risks of false positives and false negatives

2) Competence in regulatory requirements - vendor should:
   • Have complete understanding of USP <71>
   • Help you understand how to comply with regulations
   • Have products which support compliance

3) Look for variety
   • Different applications (i.e. membrane filtration, direct inoculation, closed systems and rapid sterility testing)
   • Sampling configurations designed for your product container

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4) Consider the Vendor’s Services
   • Ensure vendor has a comprehensive program to repair, calibrate and maintain any equipment
   • Provide help designing the right test method

5) Ask for Support – the vendor should:
   • Provide product training service and knowledge
   • Have experts to help you implement your sterility test
   • Provide continued support via phone & email

   • Good service and support should have you up and running quickly

   • It should be easy!

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Upcoming Webinars

- April 24th - Compounding Pharmacies and Contract Testing Lab
- May 22nd - Compounding Pharmacies and the Bacterial Endotoxin Test

THANK YOU FOR YOUR ATTENTION

QUESTIONS?

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