COMPounding PHARMACY INSPECTIONS: WHAT YOU MUST KNOW TO PREPARE FOR THE FDA

By: Steven G. Richter Ph.D.
COMPOUNDING PHARMACY INSPECTIONS:
WHAT YOU MUST KNOW TO PREPARE FOR THE FDA

INTRODUCTION

In September 2012, New England Compounding Center¹ (NECC) initiated a recall regarding its sterile methyl prednisolone, already in use with patient populations throughout the United States. According to news reports, patients who consumed the medication contracted fungal meningitis and, in some cases, died. The reports indicated that the fungal contaminant was found in unopened vials of methyl prednisolone at the compounding facility. The U.S. Federal Drug Administration (FDA) inspected the compounding facility and found issues with its environmental controls and equipment validations.

News coverage made it widely known that companies such as NECC have been performing batch drug production as compounding facilities rather than as manufacturers. Operating as such, they did not appear to fall under the scrutiny and regulation of the FDA. Current law allows the FDA to become engaged once a safety problem surfaces. However, because of the case, it appears that new FDA regulations may now cover inspections of large-scale compounders’ (LSC) operations. Now these facilities will face diligent inspections from both the state regulatory authorities and the FDA. In anticipation of new FDA regulations, many compounding pharmacies are actively working to correct any outstanding issues and attain USP <797> compliance.

This white paper addresses the issues that compounding pharmacies must resolve prior to undergoing an FDA or state inspection that specifically targets sterile compounding.

STERILE COMPOUNDING REGULATIONS

The USP section <797> Pharmaceutical Compounding — Sterile Preparations² denotes the conditions and practices to prevent harm and death to patients that could result from:

1. Microbial contamination
2. Bacterial endotoxins
3. Content uniformity: strength and correct ingredients
4. Impurities
5. Adulterated ingredients

The USP <797> document is a legal requirement for compounding pharmacies that outlines a quality program that focuses on environmental control, testing, and personnel training. One of the key focus areas is environmental control, which is required for sterile compounding (SC). SC must be performed in a clean room. All clean rooms must have controls to assure the area is operating within its design criteria. For example, if the room is designed to meet ISO 7 standards, then it should repeatedly perform to that standard regardless of challenge. The challenge can be particulate or microbial in nature, since the compounding environment is a very critical area.

Regulations indicate medium- and high-risk compounded sterile preparations (CSPs) must be compounded in an ISO 5 environment with an ISO 7 buffer area. The requirements for clean room microbial control ISO 5 are detailed in USP section <1116>³. This is an informational chapter that is referenced throughout USP <797>. Some states have their own guidelines, while others such as Massachusetts have adopted USP <797>.
Compounding aseptic containment isolators (CACIs) are utilized for toxic materials (CACIs are not covered in this white paper). Compounding aseptic isolators (CAIs) are the best choice for compounding sterile items. However, they require a vigilant microbiology and validation program. All isolators and other ISO 5 hoods used for medium- to high-risk drug compounding must be placed into an ISO 7 environment. Isolators are generally sterilized using vapor-phase hydrogen peroxide gas. The gas is introduced once the materials are placed inside the isolator — and since this practice can cause residual peroxide issues, the situation must be addressed. Therefore, isolator technology may not be the best choice for certain pharmacies. ISO 5 laminar flow benches are generally used for sterile compounding.

QUALITY TESTING

Quality testing is a separate foundation for all compounding activities. The environment must be controlled to avoid contamination. For new facilities, the critical areas should be designed by engineering professionals to meet the intended purpose. Unfortunately, many clean rooms are designed and built by contractors with little knowledge of aseptic controls and USP <797> requirements. Contamination challenges can come from the air, water, employees, raw materials, equipment, and failed HEPA filters. The aseptic compounding (high-risk) area (ISO 5) should conform or exceed USP <797> guidelines. This section covers the requirements for contamination testing and recommended action levels for microbial contamination. Section <1116> values are different than the USP <797> values. In Table 1, the values are action levels only if they trend above these values for a significant period of time.

Table 1: USP 1116 Action levels for Aseptic Environments (from USP)

<table>
<thead>
<tr>
<th>Room Classification</th>
<th>Active Air Sample (%)</th>
<th>Settle Plate (9 cm) 4 h Exposure (%)</th>
<th>Contact Plate or Swab (%)</th>
<th>Glove or Garment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolator/Closed RABS (ISO 5 or better)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>ISO 5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ISO 6</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>ISO 7</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>ISO 8</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

In any event, compounding pharmacies must prove to regulators that the environment is operating in a state of control in terms of microbiological excursions and acceptable trends and numbers. Therefore, vigilant trending of ES data is important. Inspectors will examine procedures on trending, excursions, and corrective and preventative action (CAPA). For instance, a significant excursion (>15 CFU) from the ISO 5 critical environment is indicative of an uncontrolled area. This is just one example of how the industry is moving toward USP <1116> compliance. Where <1116> makes sense for aseptic manufacturing as an additional tool, compounding pharmacies should be following <797> parenthetically using <1116> as a guideline. When excursions do exceed internal limits, then the compounding operation must be shut down and the product quarantined. The next step would be to determine the root cause for the excursion: employee, equipment, or ISO 5 contamination. USP <797> states that “Sampling Plan — an appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed.”

High-risk CSPs are required to have a high degree of assurance that contaminates are not in the environment and therefore require a restricted sampling plan. The minimum action levels for microbial contamination are shown in Table 2.
Table 2: USP <797>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Air sample per cubic meter</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO class 5</td>
<td>&gt;1 CFU</td>
</tr>
<tr>
<td>ISO class 7</td>
<td>&gt;10 CFU</td>
</tr>
<tr>
<td>ISO class 8</td>
<td>&gt;100 CFU</td>
</tr>
</tbody>
</table>

These levels are guidelines. Environmental sampling is inherently inaccurate. Therefore, percent contamination rates are more appropriate for compounding cleanrooms. For example: 0.5% contamination rate (or 99.5% free from contamination) would mean that out of 200 plates sampled, one plate had a colony. Rates of 1% or less are attainable for ISO 5 environments and garments. Due to variability and uncertainty in the measurements, alert and action levels in ISO 5 environments and garments are not recommended for aseptic processing. All microorganisms found should be identified.

Microbial contamination can come from a variety of sources. Employees are the largest contributor of bacteria and fungi. Secondly, bacterial endotoxins can contaminate CSPs from water or human sources. A robust employee training program, which includes media fills and gowning validations, must be periodically performed. All training records must be documented, including outside training. (Some states offer training funds.) Compounding pharmacies are required to maintain a state of control 100% of the time in clean room environments. Microbial and particulate air testing is to be performed during the critical operations (i.e. filling process). These data are used to support the product release and are part of the batch record. However, the data do not portend that the product is sterile. Environmental monitoring is incapable of assessing a value to sterility assurance. Sterile means the absence of viable microbial species. Aseptic means that the product was transferred to sterile container with a high degree of assurance that the personnel or equipment (clean room included) did not contaminate the product during transfer. Non-viable particulate testing should conform or exceed the ISO 14644-1 document for controlled environments. See Table 3.

Table 3: USP <797>

<table>
<thead>
<tr>
<th>ISO Classification of Particulate Matter in Room Air (limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Name</td>
</tr>
<tr>
<td>ISO, m³</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>ISO, m³</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

Clean room cleaning and disinfectant validation are required by regulators. Where product manufacturing categories are frequently changed, adequate cleaning procedures are extremely important.

In all cases, inspectors will place particular emphasis on examining excursions. Therefore, significant excursions in an ISO 5 clean area, garments, gloves, etc., should occur very infrequently. If an excursion does occur, it means the sterility assurance level is less than 10⁻³. Significant action must be taken to determine the acceptability of the batch processed during the excursion timeframe. A microbiologist or consultant microbiologist must be called on to determine next steps — which must include a corrective action and disposition of the
If the root cause is determined, then a corrective action plan can be put in place. While it is difficult to determine the root cause for most excursions, the identification of the microorganism is imperative. Microorganisms should be identified to rule out objectionable organisms, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungus etc.

**STERILITY TESTING OF COMPOUNDED ARTICLES**

To comply with the legal requirements and USP <797> document, USP <71> Sterility Tests must be followed. According to reports, NECC sent out only two vials to be tested. If so, this sample size is not appropriate according to USP <71>. It is imperative for labs to be qualified and in FDA compliance.

**DISINFECTANT VALIDATIONS**

Disinfectants are not all encompassing for microbial death. The disinfectants used in clean rooms and bench surfaces must be validated. Disinfectant validations are costly and require environmental isolates and coupons that are the same substrates as the environment. Regulators demand proof that the disinfectant is appropriate for its intended purpose of killing microbes found in the clean rooms and hoods.

Some commonly used disinfectants are listed in appendix II USP <797>. The Spaulding classification for disinfectants found in the FDA guidance documents references the following:

- **HLD:** High-level disinfectant or sporicide: peracetic acid/hydrogen peroxide
- **ILD:** Intermediate-level disinfectant: Vesphene™ or LPH (phenolics and NA hypochloride products)
- **LLD:** Low-level disinfectant: sterile 70% IPA or quaternary ammonium compounds

The use of these disinfectants is very important to the sterility assurance level of compounding products. The sterility assurance level for aseptic processing is $10^{-3}$, meaning one non-sterile in 1000 products processed. Terminal sterilized products have a sterility assurance level of $10^{-6}$. Employing a robust environmental and employee training program should result in higher levels for health, safety, and risk analysis. Quality by design (QBD) techniques can be used for determination of sterility assurance levels in a compounding operation. Regulators will ask for these types of analyses and sampling plan requirements when auditing a facility. Sampling plans should be based on a statistical rationale and be thoroughly defensible. Plans such as Mil Standard, C=0, or ISO 2859 are recommended.

Compounding pharmacies are required to provide employee training programs. The FDA and state regulators will evaluate these programs and associated training records for UPS 797 compliance. Also worth noting, gowning validation studies and media fill records and frequency must be documented. Furthermore, important for training are the assessment forms for hand hygiene, garbing, and aseptic technique located in USP <797> appendix II. See Table 4 for the USP <797> minimum frequency requirements of cleaning and disinfecting compounding areas.

**Table 4: USP <797> Minimum Frequency Requirements of Cleaning and Disinfecting Compounding Areas**

<table>
<thead>
<tr>
<th>Site</th>
<th>Minimum Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5 Primary Engineering Control</td>
<td>At the beginning of each shift, before each batch, not longer than 30 minutes following the previous surface disinfection when ongoing compounding activities are occurring, after spills, and when surface contamination is known or suspected</td>
</tr>
<tr>
<td>(e.g., LAFW, BSC, CAI, CACI)</td>
<td></td>
</tr>
<tr>
<td>Counters and easily cleanable work surfaces</td>
<td>Daily</td>
</tr>
<tr>
<td>Floors</td>
<td>Daily</td>
</tr>
<tr>
<td>Walls</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Monthly</td>
</tr>
<tr>
<td>Storage shelving</td>
<td>Monthly</td>
</tr>
</tbody>
</table>
Media test kits should be performed as prequalification testing for each employee prior to any filling activities. This training is critical and should be well thought out and documented as being the worst case. However, the value of media kits is limited and it’s best not to rely upon them for sterility assurance. We have found that negative results on media control kits do not equate to robustness or ruggedness in sterile compounding.

High-risk activities require media kit testing every 6 months. Initially, perform the media fills every month and then back down if environmental trending supports a reduced sampling plan. Every 6 months is much too long for an assessment of sterile aseptic filling operator techniques and environments. For instance, if excursion occurs, (media kit positive), everything produced up to and after the date of the last negative media fill is suspect. Consequently, a 6-month period between tests is insufficient for large compounding operations.

If materials are filtered sterilized and not compatible with steam sterilization, then a risk analysis should be performed. Aseptic processing is a high-risk activity and should not be undertaken lightly. The FDA may promulgate its Aseptic Processing Guidelines into the USP <797> documents in the wake of the NECC case. These guidelines encompass many of the same processes the USP <797> document covers. While changes may occur, the Guidelines will meet the requirements of the FDA Good Manufacturing Practices (GMPs) and USP <797> documents. A strong quality-assurance foundation is a critical platform for safe compounding pharmacy operations.

Sterilization validations support the sterility assurance level of the product. The FDA requires a sterility assurance level of one non-sterile in one million processed. This level is operational for both dry heat and steam. Some products are degraded by steam and should be tested for potency and impurities as part of the validation program. Steam sterilizers require a large amount of maintenance in order to run properly. A GMP steam sterilizer with clean steam must be used.

Beyond-use-date (BUD) testing is important for efficacy and potency. As drugs age, they become less potent and have more degradation — potentially resulting in products and impurities that may harm patients. Therefore, it is important to test the CSPs for stability using the ICH guideline. The guideline indicates the times and temperatures to test for appropriate stability results. Common concerns are potency changes and pH issues. The container closure system should also be validated at this time.

BUD activities can be difficult to manage in a compounding pharmacy. General CSPs are used quickly. When products require a shelf life, be sure the API is stable throughout the shelf life. The manufacturer may be called to determine applicability as USP <797> indicates that manufacturers are responsible for the quality of the CSP in the patient-care setting until it is administered. Therefore, the labeling is important to document the storage conditions and BUD.

**ENDOTOXIN TESTING**

The FDA requires endotoxin testing for injectables to be endotoxin free (a USP monograph will indicate such). Products used intraocular, intrathecally, and intravenously all require testing for endotoxin. Most GMP labs test for endotoxins. The regulators will review USP requirements for sample size and validation. Manufacturers must submit the required three-lot sample to the lab for inhibition enhancement testing prior to release testing. The release testing sample size depends on the lot size and should be between 3 and 10 units.

**SUMMARY**

In the aftermath of the NECC case, FDA and state actions regarding compounding pharmacies are relatively certain: regulations and inspections will both tighten and increase. The FDA, in some instances, will assume the role of lead auditor for the compounding pharmacy’s operations.

Where are compounding pharmacies to start? Step 1 is a risk analysis and quality plan. Conducting a risk assessment can be done in-house or by a third party. The robustness of a sterile product processing program is attainable through increased surveillance and education.

In the future, USP <797> section may be blended with GMP (21 CFR 211) for the FDA to better control the risk associated with compounding sterile drug products. It remains to be seen if this control improves outcomes in terms of sterility assurance.
Regardless, it is critical for compounding pharmacies to maintain a state of control in their controlled environments. While there may always be excursions, it is the actions that are undertaken after the excursions that will influence an inspector’s responses and observations during an on-site investigation and inspection.

References
1. New England Compounding Center, Framingham, Massachusetts
2. USP <797> — Pharmaceutical Compounding — Sterile Preparations
3. USP 1116 Guidelines — Microbiological Control and Monitoring of Aseptic Processing Environments
4. ISO 14644-1 — 1999, Cleanrooms and associated controlled environments
5. USP 71 — Sterility Tests
8. 21 CFR 211 — Code of Federal Regulations Title 21

About Microtest
Microtest Laboratories is a leader in testing services and contract manufacturing for medical devices, pharmaceuticals, and biotechnology. It was founded in 1984. The company’s expertise and flexible processes enhance product safety and security, speed time to market, and minimize supply chain disruption. Microtest’s unique single-source capability to provide testing and manufacturing solutions allows us to support a full pharmaceutical or medical device product release. Our facilities in Agawam, Massachusetts, USA include state-of-the-art aseptic manufacturing areas; analytical chemistry, microbiological, and virological laboratories; Class 100 clean rooms; onsite steam and ethylene oxide sterilization, plus depyrogenation capabilities; purified water systems; and voice/data systems.

About the Author
Steven G. Richter, Ph.D., is President and Chief Scientific Officer of Microtest Laboratories, Inc. Dr. Richter founded Microtest in 1984 after a distinguished career at the U.S. Food & Drug Administration. Under his leadership, Microtest has provided the medical device, pharmaceutical, and biotechnology industries with premier testing and manufacturing support.

For More Information Contact:
info@microtestlabs.com
(800) 631-1680
www.microtestlabs.com

1-800-631-1680
1-413-786-1680
fax: 1-413-789-4334

Microtest Laboratories, Inc.
104 Gold St
P.O. Box 848
Agawam, MA 01001

Microtest is a trademark of Microtest Laboratories, Inc. All other brands may be trademarks of their respective holders.

© 2013 Microtest Laboratories, Inc.
All rights reserved.
Printed in USA
1350003 03/13