Environmental Monitoring

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Impact of USP <797> on Environmental Monitoring

USP <797> standardizes the preparation of compounded sterile products (CSPs) and must be adhered to by pharmacies preparing CSPs. Recently, FDA has superseded <797> and invoked cGMPs (current Good Manufacturing Practices) when conducting audits of compounding pharmacies. Although many pharmacists may shudder at the mention of cGMPs, they also may be surprised to learn the differences between <797> and cGMPs are minor in relation to environmental monitoring (EM).

The intent of <797> is to provide hospital and compounding pharmacies with standardized practices to ensure CSPs are prepared in a manner that is not detrimental to the health and safety of patients, with a particular focus on averting microbiological contamination. Subsequent to its original publication, a number of alarming incidents have occurred, most notably the death of 64 patients who were prescribed preservative-free methylprednisolone and triamcinolone acetonide prepared by the New England Compounding Center (NECC). In response, Congress revised the Drug Quality Security Act (DQSA) in 2014 and established a new entity—the 503B outsourcing facility. Pharmacies not electing to register as 503B outsourcing facilities were reclassified as 503A compounding pharmacies, subject to the requirements of <797>.

Since the inception of this legislation, FDA has applied the same scrutiny reserved for 503B outsourcing facilities to certain 503A compounding pharmacies. These FDA actions have forced some 503A compounding pharmacies to either register as 503B outsourcing facilities or enhance their operations to comply with cGMPs, or severely curtail the amount of CSPs they produce. If history is an indicator of the future, the agency will increase its oversight of hospital pharmacies as well. Consequently, it behooves hospital pharmacies to protect themselves from this enhanced FDA surveillance by judiciously applying <797> principles along with some basic principles of cGMPs.

USP <797> and the Six-System Inspection Model

Similar to cGMPs, USP <797> emphasizes procedures and practices that reduce microbiological, chemical, physical, and endotoxin contamination and variability. FDA conducts cGMP audits using the six-system inspection model, which focuses on the Quality system as a whole, and the five systems that support Quality:

1. Quality system
2. Production system
3. Facilities and equipment system
4. Laboratory controls system
5. Materials system
6. Packaging and labeling system

Applying the six-system model may appear to add another layer of complexity and labor to the process, but for a pharmacy struggling to maintain compliance with <797>, using both documents (the six-systems model and <797>) actually simplifies the process of achieving compliance. Specifically, when applied to EM, the six-system model does not significantly differ from <797>, and using both demonstrates that the pharmacy is cognizant of cGMPs and applies them to <797>.

USP <797> and cGMP Commonalities

Maintaining a clean environment is essential to producing CSPs that are free from extraneous microbiological and particulate contaminants. Certainly EM activities consume time, materials, and resources, as well as create additional documentation requirements, but the practice serves to verify that CSPs are produced in scrupulously clean and sterile areas. Both USP <797> and cGMPs require concentrated EM efforts to ensure the facility is maintained in a manner that does not adversely affect the quality and safety of CSPs. The key components that need to be monitored in a compounding area are personnel, air, and surfaces.

Compounding Personnel
USP <797> and cGMPs agree that compounding personnel represent the
greatest threat to the safety and efficacy of a CSP, and as such, must be fully trained prior to preparing any type of CSP. Training should include live/electronic instructional sources, professional publications in aseptic principles, and demonstration of aseptic skills. Personnel must pass practical and written evaluations (eg, gowning procedures, fingertip testing, air and surface monitoring) and participate in successful semiannual media fills.

Individuals who do not achieve these criteria must be immediately retrained and reevaluated by expert compounding personnel to ensure all deficiencies are corrected. Media fill challenge testing, in which sterile fluid bacterial culture media is transferred via a sterile syringe and needle into a sterile container, is the most cogent method to evaluate an individual’s skills in aseptic preparation.

## Surfaces
To minimize the potential of microbiological contamination, clean, disinfected surfaces are mandatory and a written cleaning and monitoring program is required. The current industry standard practice is to use three disinfectants:

1. Sterile isopropyl alcohol for disinfection of surfaces, instruments, and gloves
2. A quaternary ammonium or phenolic product for daily and weekly disinfection
3. A sporicidal agent (eg, accelerated hydrogen peroxide) for monthly disinfection or when microbiological spores are isolated

### If history is an indicator of the future, the FDA will increase its oversight of hospital pharmacy compounding. Consequently, it behooves a hospital pharmacy to protect itself by judiciously applying USP <797> principles along with some basic principles of cGMPs.

### Air Monitoring

USP <797> and cGMPs also agree that EM begins with well-designed and well-constructed facilities, wherein the preparation area (ISO 5) is surrounded by areas of lower classifications (ISO 7, 8), thereby creating a unidirectional airflow from the ISO 5 area through the ISO 7 area to the ISO 8 area to an unclassified area (eg, corridor). A robust EM program must include non-viable, viable, and pressure differential monitoring. Non-viable monitoring is conducted with particle monitoring devices and ensures the minimization of particulate contamination.

Viable particle monitoring should be conducted with active air sampling devices, although settling plates are acceptable. An environmental sampling plan must be based on a risk assessment of the compounding activities performed. Selected sampling sites must include locations within each ISO Class 5, 7, and 8 area, and the plan should detail the sample locations, methods of collection, sampling frequencies, volume of air sampled, and time of day related to activity in the compounding area. The data must be reviewed and any upward trends investigated to ensure there are no adverse changes within the environment. Additionally, isolation of pathogenic or objectionable microorganisms must be investigated.

### Differential Pressure

Differential pressure monitoring ensures the unidirectional flow of air from high-risk (ISO 5) to lower risk (ISO 7 and 8) areas. Pressure gauges or velocity meters must be installed and the data reviewed and documented in a log every work shift (or at a minimum, daily). Alternatively, a continuous recording device can be used. The pressure difference between the ISO Class 7 and the general pharmacy area must be at least 5 Pascals (Pa) (0.02 inch water column). In facilities where low- and medium-risk level CSPs are prepared, the differential airflow must be maintained at a minimum velocity of 0.2 meters per second (40 feet per minute) between the buffer and ante areas.

### TABLE 1

#### Cleanroom Classification Limits

<table>
<thead>
<tr>
<th>ISO/Class Designation</th>
<th>cGMP Grade (EU based)</th>
<th>Non-Viable Particles ≥ 0.5 μm particles/m³</th>
<th>Microbiological Active Air Action Levels (CFU/m³)</th>
<th>Microbiological Settling Plates Action Levels (diam. 90mm; CFU/4 hours)</th>
<th>Fingertip Sample (CFU/plate)</th>
<th>Surface Sample (Contact Plate) (CFU/plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/100</td>
<td>A, B</td>
<td>3,520</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>6/1,000</td>
<td>N/A</td>
<td>3520</td>
<td>&gt;7</td>
<td>&gt;3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7/10,000</td>
<td>C</td>
<td>352,000</td>
<td>&gt;10</td>
<td>&gt;5</td>
<td>N/A</td>
<td>&gt;5</td>
</tr>
<tr>
<td>8/100,000</td>
<td>D</td>
<td>3,520,000</td>
<td>&gt;100</td>
<td>&gt;50</td>
<td>N/A</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

*Preferred method, although settling plates are not excluded.*
FDA may ultimately require they be conducted by a hospital pharmacy.

USP <797> and cGMPs require that surface sampling be performed in all ISO classified areas on a periodic basis using contact plates or swabs; <797> requires it be done at the conclusion of compound ng. Sample locations must be defined in the EM plan or on a form and should include surface wipe sampling of the working areas in biological safety cabinets (BSCs); compounding aseptic containment isolators (CACIs); counter tops where finished preparations are placed; areas adjacent to BSCs and CACIs, including the floor directly under the work area; and patient administration areas. An investigation must be conducted when trends or pathogens/objectionable microorganisms are found.

Justifying EM Frequency
Under USP <797> and the six-system model, a pharmacy must demonstrate control of microbes and particles through a robust EM program, starting with a written plan for differential pressure monitoring, non-viable particle counts, and viable particle counts to assess the functionality of the air handling system. To assess the competency of the individuals preparing CSPs, the plan must incorporate personnel and surface monitoring, including monitoring frequency and sample locations, as well as limits for non-viable and viable counts, surfaces, and gloved fingertips.

The expectation, both in <797> and cGMPs, is that microbiological and non-viable particles in Class 5 areas (eg, LAFWs, BSCs, CAIs, and CACIs) must be within the specified limits. TABLE 1 summarizes acceptable limits for each type of classified room, as defined by ISO and European Union cGMPs.

Likewise depicted in TABLE 1, both USP <797> and cGMPs require that fingertip and glove samples be performed during every operation that is conducted in a Class A area (ie, where CSPs are produced). In contrast, the frequency of surface, air, and non-viable monitoring differs between the two documents, as cGMPs require these samples be obtained during every operation, and <797> requires air sampling be performed at least semiannually and surface samples be obtained on a periodic basis. Although hospital and 503A pharmacies would be technically correct to apply <797> sampling frequency requirements, the reality is that FDA has raised the expectation of increasing the sampling frequency to mimic that of cGMPs. This creates a conundrum that can be solved through data generation.

Empirical data can be used to justify alternative frequencies that differ from cGMPs or <797> if they are generated by clearly defined, protocol-driven studies. For example, a protocol-driven study to show equivalency between <797> and cGMPs sampling frequencies could be drafted that would include the following:

1. Conduct EM for every CSP prepared over a defined period of time (eg, 6 months)
2. Determine trends that occurred outside the limits in TABLE 1
3. Determine the risk if reduced EM was conducted
4. Reduce the EM frequency based on the risk (eg, 3 days each week)
5. Further reduce the EM frequency based on additional data obtained during a specified time period (eg, 2 months)
6. Increase the EM frequency for a specified time if data show an increase in trends outside the limits in TABLE 1
7. Reevaluate the frequency after completing step number six

Drafting and successfully executing the protocol will support reduced monitoring as required by <797> while also satisfying the cGMP requirement of conducting EM for every CSP. The salient point is that a science-based approach can enable a hospital or compounding pharmacy to be compliant with the sampling frequency requirements for both <797> and cGMPs.

Regulatory Divergence Between USP <797> and cGMPs
The requirements of cGMPs are general and provide an overview of what is necessary for manufacturing facilities to produce safe and efficacious products. Interestingly, <797> sometimes provides more details than cGMPs.

HEPA Filter Leak Test
HEPA filtration, for example, is not mentioned in cGMPs and the only reference to air filtration is in section § 211.46 Ventilation, air filtration, air heating and cooling: (c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants. In contrast, <797> states: All HEPA filters shall be efficiency tested using the most penetrating particle size and shall be leak tested at the factory and then leak tested again in situ after installation.

However, FDA fills this and other cGMP voids by publishing Industry Guidance reports. For example, the Aseptic Processing guidance includes a section on HEPA filtration that recommends performing leak
testing for each HEPA filter twice a year; USP <797> does not provide a definitive frequency for conducting leak testing. In this instance, FDA may expect a hospital pharmacy to follow cGMPs (the Aseptic Processing guidance) and conduct leak testing twice a year. Considering that HEPA filters produce unidirectional air that contacts surfaces and components used to prepare CSPs, this expectation is not unrealistic and should be adopted by pharmacy to ensure CSPs are not subject to extraneous airborne contaminants.

**Pressure Differentials**

A similar situation exists with differential pressures. USP <797> includes a section entitled, Pressure Differential Monitoring that states, A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column). In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meters per second (40 feet per minute) between buffer area and ante-area.

The cGMP Aseptic Processing guidance also includes a section on pressure differentials and mentions the term numerous times. For example, it states, An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent, less clean areas. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. For example, a positive pressure differential of at least 10-15 Pascals (Pa)

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1. Dr. Alan-Shaun Wilkinson. ASHP 2014 presentation. Towards Extending the Practical Shelf Life (EPSL) or Beyond Use Date (BUD) for hazardous drugs in Preservative Free Single Dose Drug Vials (SDV) using OnGuard™ system.


3. Minimizing the Risk of Exposure to Potentially Hazardous Drugs, Souraski Medical Center, Tel Aviv, Israel, October, 2010.

4. Evaluation of a closed-system cytotoxic transfer device in a pharmaceutical isolator. N Vyas, J Oncol pharm Practice 0 (0) 1-11 2014.


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Environmental Monitoring

should be maintained between adjacent rooms of differing classification (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and it is critical that the time a door can remain open be strictly controlled.

Given that cGMPs may be more stringent than USP <797>, it may appear that following cGMPs imposes an unnecessary burden. However, most BSCs and LAFWs are designed to achieve differential pressure and air flows that adhere to cGMP requirements, and a pharmacy simply needs to have these measurements certified twice a year to demonstrate that they are compliant with both USP <797> and cGMPs.

Smoke Testing
USP <797> and cGMPs differ on smoke studies, but the differences are minor. For example, USP <797> states, In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. Whereas, the Aseptic Processing guidance states, Smoke studies and multi-location particle data can provide valuable information when performing qualification studies to assess whether proper particle control dynamics have been achieved throughout the critical area. As neither document provides details related to frequency, compliance to both documents can be achieved by conducting smoke studies during initial installation and after each biannual leak test that does not meet the recertification requirements.

Conclusion
The pressure on hospital pharmacies to ensure compounding operations are compliant is only increasing as regulators, from state boards of pharmacy to accrediting agencies, are inspecting compounding practices and expecting compliance to USP <797> and, in some cases, cGMPs. Even hospital pharmacies that operate as 503A facilities should be cognizant of cGMP requirements. In fact, the close similarities between USP <797> and cGMPs related to environmental monitoring provide a strong argument for hospital pharmacists to not only educate themselves on both regulations, but also to consider implementing EM practices that achieve the aims set forth in both documents.

Part 2 of this article, Regulatory Requirements for Environmental Monitoring Trending with Excursions, will address environmental monitoring trending with a strong focus on how to identify and remediate excursions outside of the established limits.

References
5. USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations.

Frank Settineri, BS, MS, has over 30 years’ experience working with a range of entities from compounding pharmacies to pharmaceutical companies, focusing on investigations, root cause analysis, microbiological data deviations, particulate matter mitigation, and cGMP compliance. He is particularly adept in writing responses to 483s and warning letters that result in both interim controls and sustained cGMP compliance. Frank is president and founder of Veracorp LLC, a consulting firm with a client base including compounding pharmacies, sterile facilities, API manufacturers, oral dosage manufacturers, and microbiology laboratories.