

The Microbial Bioburden of USP 797 Compliance

Simplifying Environmental Quality and Control Practices
for Pharmaceutical Compounding

PathCon Laboratories
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USP Regulation 797

The Standard for Compounded Sterile Preparations (CSPs)

What is USP Regulation 797?

Issued by the nonprofit United States Pharmacopoeia (USP) and endorsed by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), USP Regulation 797 is the first enforceable standard for sterile compounding. Originally enacted on January 1, 2004, the latest revision became official on June 1, 2008.

USP 797 is a broad regulation that covers a variety of pharmacy policies and procedures. It is designed to reduce the number of patient infections due to contaminated pharmaceutical preparations.

This paper focuses on quality and control aspects of USP 797 as they relate to the immediate environment in which compounded sterile preparations (CSPs) are prepared. USP 797 contains specific requirements for ongoing air and surface evaluations to ensure product sterility and safety. Increasingly, affected organizations are realizing the importance of USP 797 compliance.

Why is Such a Standard Needed?

USP 797 was developed in response to real-world situations where patients were sickened by contaminated CSPs. One of the most notable examples occurred in 2006 at Mary Washington Hospital in Fredericksburg, Va., where 11 cardiac surgery patients became ill over a 10-month period, and three died. Health officials later identified the cause to be a CSP solution containing bacteria that was injected into patients' hearts during surgery.

Since then, there have been multiple instances where similar contaminations have impacted patient health. USP 797 sets into place the proper procedures for compounding sterile preparations, in order to mitigate risks. The standard is enforceable primarily by state boards of pharmacy and boards of health, and in some cases by the Food & Drug Administration (FDA).

As part of USP 797, environmental quality and control practices – those relating to airborne and surface bacteria – are vital.

Who Needs to be Concerned About USP 797 Compliance?

USP 797 applies to all personnel who prepare CSPs and all places where they are created – including hospitals, clinics, pharmacies and physician offices. Such sites tend to have less formal procedures in place to safeguard sterility as compared to those that govern commercial drug manufacturers.

Pharmacy-made compounds account for about one to five percent of all prescriptions today. Common examples of CSPs include inhalants, injections, soaks for live organs and tissues, intravenous solutions, chemotherapy drugs, irrigation solutions, and ophthalmic drops and ointments. Such preparations are made on-site either because they are not made commercially, or because a custom mixture is required to meet patient needs.

What is the Cost for USP 797 Compliance?

Costs related to USP 797 compliance can vary greatly – from minimal costs that support basic hygiene and environmental monitoring practices to, in some cases, larger investments in equipment required for sterile compounding, such as laminar air flow workbenches (LAFW), biological safety cabinets (BSCs), or other primary engineering control (PEC) devices.

Your facility's specific needs will depend on your current compounding environment, as well as the types of CSPs being prepared. A key consideration, however, is the cost of *non-compliance* in the event that a contamination is tracked to your facility.

USP Regulation 797

Environmental Quality and Control Aspects

Some of the questions pharmaceutical compounders are asking about environmental (i.e., microbiological) testing include:

- What are CSP risk levels?
- How do I test for contaminants in the areas where CSPs are prepared?
- Are both identification and colony counts of microorganisms necessary?
- What is the appropriate frequency of sampling?
- What actions should be taken if microbial contamination is detected?
- Should sampling and testing be done in-house or outsourced?

Remember that monitoring air quality and surface cleanliness of the area in which you are compounding is only one aspect of USP 797 compliance. Other factors include hand hygiene and garbing procedures, proper labeling and storage of ingredients, and adequate training of all personnel preparing or handling CSPs. However, environmental quality and control are among the most complex requirements.

Determining CSP Risk Levels

There are three risk levels for CSPs: low, medium and high. Each category is assigned based on the potential for microbial contamination, as well as for foreign chemical and physical contamination, during compounding activities. Additionally, the high-risk level is assigned based on the potential for not achieving sterility of the CSP.

Naturally, requirements for compounding environments that prepare high-risk CSPs are more stringent than for those preparing low- and medium-risk CSPs. A first step is to determine the risk levels for the CSPs your pharmacy or site is preparing and follow appropriate protocols for each, including for air and surface sampling.

As part of this, critical areas for compounding within your site will also require certification of workspaces (for example, clean rooms) as ISO Class 5, 7 or 8, depending upon the risk level of CSPs being produced.

For guidance on determining CSP risk levels, including the related ISO classification requirements, see Appendix I to this document beginning on page 11.

Environmental Sampling – Air and Surface

Air and surface sampling in areas where compounding is taking place is a key requirement for USP 797 compliance. Compounding areas to be considered for evaluation include ISO Class 5 PECs, buffer areas, ante-areas, and segregated compounding areas at greatest risk for contamination. In general, guidelines state that:

- Environmental sampling should be conducted as part of the commissioning of new facilities and certification of equipment
- Air sampling should be performed at least every six months
- Surface sampling should be conducted on a periodic basis
- Environmental sampling should be initiated as a reaction to recognized problems with end products, personnel work techniques or patient-related infections.

It is important to note that with regard to air quality, many compounding pharmacies have more frequent sampling programs in place. In fact, some experts contend that the semi-annual USP 797 requirement is inadequate for microbial control.

Trained in-house staff can perform air and surface sampling, or it can be outsourced to those with specific experience, such as industrial hygiene and safety experts, controlled environment-testing technicians, or an environmental health lab specializing in controlled microbiological testing and analysis.

To test for contaminants, air sampling requires the use of a **volumetric sampler** that is capable of collecting a sufficient volume of air (the recommended volume is 400 to 1000 liters per sample) and a general bacterial or fungal culture media (depending on the risk levels of CSPs being prepared).

Surface sampling can be performed using **contact plates** with either bacterial or fungal culture media (depending on the risk levels of CSPs being prepared), or **sterile swabs**.

A qualified industrial hygienist or environmental health lab can provide further instruction on air and surface sampling techniques and protocols.

If Microbial Contamination is Detected

If pathogenic microorganisms are detected and exceed the concentration action levels as defined by USP 797, compounding sites must take action. In most cases, this requires only basic measures such as wiping surfaces with a disinfectant or re-evaluating proper garbing or hand hygiene practices. In less frequent cases, a more thorough evaluation of the compounding environment may be required, including a

review of air filtration system efficiency or the installation of new equipment. When microbial contamination is found, air and/or surface re-sampling must be performed to verify that identified problems have been eliminated.

Microbial Action Levels

Viable Air Sampling

Recommended Action Levels for Microbial Contamination

Classification	Count (CFU/m³)
ISO Class 5	>1
ISO Class 7	>10
ISO Class 8 or worse	>100

Surface Sampling

Recommended Action Levels for Microbial Contamination

Classification	Surface Sample (CFU per plate)
ISO Class 5	>3
ISO Class 7	>5
ISO Class 8 or worse	>100

In the event that air or surface microbial contamination action levels are reached, taking immediate action will help to quickly eradicate threats and mitigate risks to patient health. In certain cases, it may be necessary to consult with an infection control specialist to identify and correct the source of contamination.

Other Considerations

USP 797 presents a notable change for many compounding sites, including those with environmental air and surface sampling practices already in place.

Two of the impacting factors include:

- Volumetric air samples are now required over the use of settling plates for assessing microbial air contamination. Although volumetric samplers are relatively easy for personnel to use with some training, the equipment itself is costly and also requires maintenance and calibration on a regular basis; therefore, rental of sampling equipment may be a better choice.
- Compounding sites are also now required to identify the types of microorganisms that are contained in air and surface samples, in addition to the microbial concentration. While the latter can be performed with the naked eye, accurate identification of microorganisms requires specialized knowledge.

The next section of this paper discusses the benefits of using qualified industrial hygiene experts and credentialed environmental health laboratories to assist in USP 797 air and surface testing and compliance.

Selecting and Working with Environmental Health Experts

Sampling, Analysis and Guidance

Compounding sites may find it more economical and efficient to partner with technical experts in the field of environmental health like industrial hygienists and credentialed analytical laboratories to fulfill their microbiological sampling and testing requirements for USP 797 compliance.

For hospital pharmacies in particular that have access to on-site clinical laboratories, it might seem that conducting such analyses in-house is a better option. However, consider these facts:

- Most clinical labs in hospital environments are already overworked and are often backlogged with patient samples for testing. In these cases, adding to their analyses burden just isn't practical.
- Hospital clinicians generally do not have experience in identifying and analyzing environmental contaminants, requiring additional education and training.

Qualified environmental experts can provide you with the specific level of assistance your site needs. In many cases, compounding sites will opt to conduct their own air and surface sampling using products and equipment provided by the environmental health lab, and then send the samples to the lab for proper testing. Some environmental health labs and industrial hygiene firms can also go beyond this to provide comprehensive on-site services that include air and surface sampling and troubleshooting in the event that a contamination is detected.

Some of the products and services an environmental health lab may offer include:

- Custom sampling protocols and schedules and chain-of-custody forms
- Volumetric air sampler rental
- Microbiological air sampling media and contact plates or swabs for surface sampling
- Shipping containers and forms
- Lab support, including microbial identifications and bacterial/fungal colony counts
- Consulting, guidance and rapid response to contaminations

For a real-world scenario that illustrates how a compounding facility might work with an environmental health lab to achieve USP 797 compliance, see Appendix II beginning on page 13.

What to Look For in an Environmental Health Laboratory

A qualified environmental health lab should be recognizable by its experience, credentials and the accreditations of its personnel. It will also specialize in laboratory analyses designed to help clients meet the requirements specified in USP 797. As part of this, the lab should focus specifically on environmental bacteria and fungi, and be able to offer protocols and guidelines relating to the collection of these organisms.

Importantly, some labs provide only test results back to clients – in other words, they provide only the raw data. The environmental health lab you choose should have experience both in helping clients to test microbial air and surface samples, *and* in interpreting the results. In this way, you are better able to understand your situation and more effectively control potential hazards.

With USP 797 compliance comes the peace of mind that your pharmaceutical compounding environment is sterile and that you are contributing to the overall assurance of patient safety and health. Although the steps required may require new operational practices, they are necessary steps that must be taken.

Partnering with the right environmental health experts is one way to ease the microbial bioburden of compliance.

Appendix I: Determining CSP Risk Levels

There are three risk levels for CSPs: low, medium and high. Each category is assigned based on the potential for contamination during compounding activities.

Low-Risk Level CSPs

Low-risk compounding takes place in an ISO Class 5 environment and requires only a few basic, closed-system steps.

Some examples of low-risk CSPs include:

- Reconstituting single-dose vials of antibiotics
- Preparing hydration solutions
- Compounding CSPs from sterile commercial drugs using commercial sterile devices

Standard safety measures should include:

- Routine disinfection and air quality testing to maintain ISO Class 5
- Proper and adequate safety clothing
- Component review before and after compounding
- Visual inspection of each sterile preparation as a final step

ISO air classification recommendations:

- CSPs should be prepared in an ISO Class 5 primary engineering control (PEC) device inside of an ISO Class 7 or ISO Class 8 clean room
- Ante room leading into clean room should be ISO Class 8

At this level, your site will need to complete an annual media fill test.

Medium-Risk Level CSPs

Medium-risk level compounding involves more complex procedures that may occur over an extended time period. It also incorporates pooled sterile commercial products for multiple patients, or for one patient multiple times.

Some examples of medium-risk CSPs include:

- Chemotherapy or pain management administered by an infusion device
- Pooled admixtures
- Batched antibiotics
- Total parenteral nutrition solutions using automated or manual compounders
- Batch compounded preparations that do not contain bacteriostatic components

Standard safety measures should include:

The same safety procedures apply as the low-risk level. However, compounding environments must undertake a more challenging annual media fill evaluation that simulates more complex/stressful conditions.

ISO air classification recommendations:

- CSPs should be prepared in an ISO Class 5 PEC inside of an ISO Class 7 clean room
- Ante room leading into clean room should be ISO Class 7

High-Risk Level CSPs

High-risk level compounding occurs when CSPs are prepared from non-sterile ingredients, or when CSPs are prepared from sterile ingredients but the air quality is not ISO Class 5. It also occurs when more than six hours passes between compounding and sterilization steps.

Some examples of high-risk CSPs include:

- Preparing CSPs from bulk, non-sterile components
- Open storage of sterile ingredients and devices in an environment below ISO Class 5
- Using final containers that are non-sterile and must be terminally sterilized

Standard safety measures should include:

The same safety procedures apply as to the low- and medium-risk levels. However, at this level, compounding sites must undergo a semi-annual media fill evaluation that simulates the most complex/stressful conditions and uses dry, non-sterile media verification.

ISO air classification recommendations:

- CSPs should be prepared in an ISO Class 5 PEC, inside of an ISO Class 5 clean room
- Ante room leading into clean room should be ISO Class 7

Appendix II: Working with an Environmental Health Lab

Client: Acme Drug Manufacturer
Business: Drug manufacturer

Product: Reconstituting single dose vials of antibiotics
Risk Level: Low
ISO Class: 5

Background:

Acme performed no environmental testing prior to USP 797, and the company was unsure how to tackle the issues surrounding the microbial burden of the regulations: where to test, when to test, who in the company should do the testing, how to test, how to interpret results and how to fix potential problems.

Solution:

Employees from Acme's facilities management division reviewed an environmental health laboratory's program online and approached the company to provide testing and analytical support at their facility.

Results:

The environmental health laboratory sent Acme an air sampler, appropriate media and guidelines for testing. Acme took the samples as instructed and sent the samples back to the lab for analysis. After review of the samples, it was determined that ACME had no environmental contamination at their CSP compounding site.

Acme is on a quarterly monitoring program with the environmental health laboratory that performed the testing and analysis and is able to efficiently and cost-effectively comply with USP 797 guidelines, while ensuring the most sterile CSPs possible for clients.

Client: ABC Hospital Pharmacy
Business: Healthcare facility, focus on cancer treatment
Products: Chemotherapy/pain management administered by infusion device
Risk Level: Medium
ISO Class: 7

Background:

ABC began environmental testing in 2007 to ensure that sterile CSPs were being made in the hospital pharmacy for use with the hospital's chemotherapy patients. The hospital lab provided the necessary analysis (colony count) of samples taken by pharmacy personnel via a rented air sampler. However, the bi-annual samples became backlogged due to the hospital lab's priority of clinical samples. In addition, new USP guidelines called for environmental pathogen identification **in addition to** colony counts – a skill not found among the clinical microbiologists in the hospital lab.

Solution:

Hospital administrators met representatives from an environmental health laboratory at a pharmaceutical industry conference. They contracted the laboratory to provide the appropriate media and air sampler, and to conduct laboratory identification and analysis of environmental pathogens in their pharmacy.

Results:

After an initial round of testing, high levels of *Pseudomonas* were detected in the CSP prep area through an analysis and identification by the environmental health laboratory. The suspected source of the bacteria was quickly sanitized, and sampling was completed again. The second round of testing detected no trace of the bacteria.

Post Results:

When a chemotherapy patient became ill at ABC Hospital, it was suspected that the CSP provided by the hospital's pharmacy was contaminated. The pharmacy was quickly able to test and eliminate the batch of drug indicated; **as well as** provide documentation that the pharmacy was regularly tested for environmental pathogens and had a clean record as of the batch date of the drug indicated.

ABC Hospital participates in a monthly program with the environmental health laboratory that performed its testing and analysis, ensuring the most up-to-date results for facility sterility.

About PathCon

PathCon Laboratories, the pathogen control experts, was founded in 1986 by former CDC scientists to provide services in indoor air quality for the private sector. The company has since evolved into one of the nation's most respected outbreak, laboratory and consulting resources. It provides Fortune 500 companies, environmental health firms, engineering firms, industrial hygienists, hospitals, pharmacies and the hospitality

industry with expertise in microbiology, infectious diseases, epidemiology, medicine, and disease prevention. PathCon's world-renowned experts make the decisions that craft government policy and industry standards that other labs follow. PathCon delivers the most accurate, high-quality, expert laboratory analysis and consulting to its clients, setting the lab-testing standard for the life sciences industry.

For information on PathCon's comprehensive services that support USP 797 compliance, visit www.pathcon.com.