Baxa Corporation

Environmental Controls for Sterile Compounding

Technical Paper

A guidance document on developing sterile preparation areas to meet the USP <797> requirements for low and medium risk compounded sterile preparations (CSPs).

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Abstract

This paper provides clarification and possible alternatives for designing room layouts, engineering controls, and equipment that provide the necessary level of environmental control to satisfy the requirements for compounding sterile preparations in compliance with USP 797. The standard is presented in sections that include: compounding personnel responsibilities, risk level classifications, verification of compounding accuracy/sterility, quality assurance and quality control, event and patient monitoring, training and evaluation, and environmental quality and control. This paper addresses environmental quality and control issues.

Introduction

USP Chapter <797>, released in January 2004, created a new (US) national standard for sterile preparation. The standard resulted from the efforts of earlier organizations to improve the quality and consistency of sterile preparations. These groups included the National Coordinating Commitee on Large Volume Parenterals (NCCLVP), the American Society for Health-System Pharmacists (ASHP) Guidelines, USP Chapter <1206>, FDA Modernization Act of 1997 (FDAMA) and the National Association of Boards of Pharmacy (NABP). The new standard is intended to describe the current best practice for quality assurance in compounding in an effort to improve patient safety and reduce the number of adverse events related to compounding activities.

There is still debate within the pharmacy profession about what the requirements are to fully comply with this new standard. However, what individuals can agree on is that the practices of the past are going to change, particularly in hospitals. The extent of change necessary to achieve "excellent" results will be determined over time as the Chapter guidelines are interpreted and individual (facility) responses are audited for compliance. Refer to the USP Web site (www.usp.org) and the *JCAHO Perspectives* newsletter (www.jcaho.org) for current guidance on the regulations.

Understanding Cleanrooms

The International Standards Organization (ISO) defines a cleanroom as, "A room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particulates inside the room, and in which other relevant parameters, e.g., temperature, humidity, pressure, are controlled as necessary." Control in this context means that a selected parameter is governed by procedure and practice, is routinely measured, and prescribed action is taken if that parameter exceeds predetermined limits.

ISO 14644 classifies nine levels of cleanroom based upon particle counts within one cubic meter of room air. ISO Class 1 is the highest or cleanest rating, with Class 9 being the lowest. A number of third-party vendor offer particle counting services. There are also cleanroom particle counters

available for sale that can be used to evaluate the cleanliness of sterile compounding preparation areas. The *Cleanrooms* (http://cr.pennnet.com/home.cfm) and *Cleanroom Technology* (http://www.cleanroom-technology.co.uk/) magazine Web sites both offer references and resources for determining current state of environmental control, as well as information on designing and constructing cleanrooms, and purchasing cleanroom equipment.

Requirements

USP 797 requires that low- and medium- risk compounded sterile preparations (CSP's) be prepared in a 'suitable' area. The document provides guidance for establishing controls over CSP production and processes. It also includes some recommendations for how to meet the requirements.

In a hospital pharmacy context, USP <797> requires the maintenance of ISO Class 5 air quality for the sterile compounding area. This designation, formerly Class 100, allows a maximum of 100 particles per cubic foot. This environmental control is the same level as the typical laminar airflow hood (LAFW) in use in US pharmacies today. The Chapter also allows the use of verified alternative systems in cleanrooms that achieve the same or better level of environmental controls as LAFWs.

In addition to the primary engineering control above, USP 797 requires secondary engineering control that provides a buffer zone around the primary mixing area. This buffer zone should be preceded by an anteroom that is a clean area for putting on personnel barriers such as hair covers, gloves and gowns. The class limit for this buffer zone should be demonstrably better than ambient air, providing at least Class 8 air quality. This class, formerly Class 100,000, allows a maximum of 100,000 particles per cubic foot.

Baseline testing should be performed in these designated areas to determine the current level of environmental contamination before undertaking construction and redesign projects. Implementing basic cleaning and control steps, coupled with a positive pressure air system, mayresult in a room with less than 10,000 particles per cubic foot. Then, the standard of less than 100,000 particles per cubic foot is achievable by following the simple USP 797 physical facility suggestions.However, in practice there are different options regarding the establishment and maintainance of these production and process controls in the pharmacy.

Basic Requirements

There are a number of options for meeting the USP 797 guidelines as they are currently described. Three such options (Good, Better, Best) are detailed in the examples below. This guidance is not intended to dictate how a preparation area for low and medium risk CSP's must be laid out, but to provide some options for satisfying the USP requirements.

The elements below are basic production and process controls that are required for all CSP production areas. Please note that these requirements address environmental control for compounding *standard* sterile preparations for IV administration. There are separate recommendations for safe handling of hazardous drugs that should be reviewed and addressed prior to undertaking a facility redesign.[8]

1. ISO Class 5 Air Quality in the critical area.
   Primary environmental control must provide at least ISO Class 5 quality of air to which sterile ingredients and components of CSP's are directly exposed.[7]
2. Environmental Controls and Procedures
   a. ISO Class 8 air quality in the buffer areas
   b. Area entry
   c. Materials movement and storage
   d. Gowning, hair covers, etc.
   e. Hand washing
   f. Behavior
   g. Area clearance between batches
   h. Area exit
3. Housekeeping Procedure
4. Visual Controls
5. Microbial and Particulate Monitoring

"Good" Sterile Preparation Controls

1. All the *Required Items* shown above.
2. A *Controlled Environment Area* of the Pharmacy where CSP's are made, ingredients are opened, etc. This area of the pharmacy is not necessarily a separate room, but is isolated and well-marked, using clear visual controls such as floor tape, paint, physical barriers, etc.
3. *Laminar Air Flow Workbench(es), Vertical Flow Clean Bench(es), Biological Safety Cabinet(s), or Barrier Isolator(s)* certified to provide ISO Class 5 Air Quality. This is where the actual CSP compounding takes place.

"Better" Sterile Preparation Controls

1. All *Required Items* shown above.
2. A dedicated *Controlled Environment Room*. This room is closed off from the rest of the pharmacy by standard structural features such as doors and walls. This "white room" is isolated, and accommodates all of the items found in #2 of the Required Items above.
4. *Laminar Air Flow Workbench(es), Vertical Flow Clean Bench(es), Biological Safety Cabinet(s), or Barrier Isolator(s)* certified to provide ISO Class 5 Air Quality. This is where sterile compounding takes place.

"Best" Sterile Preparation Controls

1. All *Required Items* shown above.
2. A *positive or negative pressure* cleanroom with ISO Class 8 air quality.
3. An *anteroom* for entry from the outside areas.
4. *Airlocks* or pass throughs for material movement.
5. *Hand-washing* facilities.
6. *Laminar Air Flow Workbench(es), Vertical Flow Clean Bench(es), Biological Safety Cabinet(s), or Barrier Isolator(s)* certified to provide ISO Class 5 Air Quality. This is where sterile compounding takes place.

Conclusion

Most pharmacies will have significant gaps between the USP 797 requirements and their current facilities and standards of practice. The timelines for compliance have been set forth to allow a reasonable period for gap analysis, evaluation and the development of action plans for remediation. A number of steps can be taken in order to immediately improve the practice of sterile compounding, which would reduce the risks of inaccurate and contaminated compounds. Individual facilities should move to address those requirements that would have the greatest immediate impact on CSP quality, then seek guidance where necessary from qualified (certified) consultants with regards to cleanroom design and environmental control prior to modifying existing facilities.

Additional Resources

1. The ASHP Discussion Guide for Compounding Sterile Preparations. American Society of Health-System Pharmacists. 2004. www.ashp.org.
2. Cleanroom Design: Fundamentals of Design, Testing, and Operation. Whyte, William. ISBN 0471 942049. Wiley Press.
3. Control of Particulate Contamination in Healthcare Manufacturing. Barber, Thomas A. ISBN 1-57491-072-8. Interpharm Press.
4. *Frequently Asked Questions About Cleanrooms*. Baxa Corporation Technical Paper. Hynes, J. Patrick.
5. HEPA Corporation. www.hepa.com
6. ISO-14644 Family of Cleanroom Standards. (8 documents). www.iso.org.
7. *USP, NF, 2004 Chapter 797.* United States Pharmaceopeia. www.usp.org.
8. *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings.* Department of Health and Human Services. DHHS (NIOSH) Publication Number 2004-165. September 2004.