

Particle Monitoring to Meet USP <797>

1. Introduction

The United States Pharmacopoeia (USP) recently released procedures and requirements for compounding sterile preparations. General chapter <797>, titled “Pharmaceutical Compounding – Sterile Preparations,” states that sterile compounding procedures require clean facilities, specific training for operators, air quality evaluations, and a sound knowledge of sterilization and stability principles. The nature of defining how these preparations shall be manufactured is related to the potential risk to patients should errors occur.

This paper reviews the requirements for non-viable particle limits and the monitoring of those areas where product is exposed.

2. Environmental Requirements

Products are manufactured according to one of three risk factors: low, medium, and high. Those products which are manufactured as an aseptic parenteral have the greatest risk of contamination, and therefore they must be manufactured in an area tolerating only the lowest level of risk. “Aqueous injections for administration into the vascular and central nervous systems pose the greatest risk of harm to patients if there are errors of non-sterility and large errors in ingredients,”¹ and therefore the greatest level of control over manufacturing must be proven. They must be manufactured under a “laminar flow clean-air hood, barrier isolator, or other contamination control device appropriate for the risk level, that provide an adequate critical site environment”.¹

Critical site environments, defined below, must prove that they meet the international standard for cleanliness to ISO14644-1 Class 5, where no more than 3520 particles at 0.5 µm are present per cubic meter of sampled air. The ISO classes will be briefly discussed in this paper.

The supporting area, or clean room areas where the laminar flow stations are located, should meet at least ISO 8 air quality. The supporting area will be discussed in greater detail below.

For a better understanding of the requirements, a document to read in conjunction with the USP <797> is the Food and Drug Administration’s (FDA) *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, September 2004*. This document identifies how the manufacturing of sterile products should be undertaken and defines certain elements of critical environments.

Defining Critical and Supporting Areas

Critical areas

The USP defines a critical area as the central location for performing sterile manipulations which should be a laminar flow, ISO 5 environment. The FDA Guidance defines it as the following:

A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility (§ 211.42(c)(10)). Activities

conducted in such areas include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations.²

The USP and the FDA share a harmonized view of both the definition of critical areas and the activities which are critical in nature. In addition, the FDA defines the limit of particles in air:

Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 µm and larger when counted at representative locations normally not more than 1 foot away from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5).²

Therefore, those activities that pose the greatest risk to final product quality must be done in an environment that meets ISO 5, again showing harmonization of the two references.

Supporting Areas

The USP defines this area as a controlled environment that minimizes the contamination of the area immediately surrounding the critical area. The FDA defines this area as the following:

Supporting clean areas can have various classifications and functions. Many support areas function as zones in which non-sterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred. These environments are soundly designed when they minimize the level of particle contaminants in the final product and control the microbiological content (bio-burden) of articles and components that are subsequently sterilized.²

The USP states that supporting areas must meet an air quality of at least ISO 8; the FDA recommends the following:

The nature of the activities conducted in a supporting clean area determines its classification. FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards (see Table 1) under dynamic conditions. Manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5). An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning).²

Again, there is harmonization between the FDA and the USP on the expectations of supporting clean areas, though the FDA is more precise in defining that the risk of each area should be assessed and a classification assigned according to that risk. The table below is an extract from the FDA guidance and can be directly compared with that shown in USP <797>. The table also identifies the maximum permissible microbiological limits for the associated manufacturing areas.

Clean Area Classification (0.5 µm particles/ft ³)	ISO Designation	≥ 0.5 µm particles/m ³	Microbiological Active Air Action Levels (cfu/m ³)	Microbiological Settling Plates Action Levels (diam. 90mm; cfu/4 hours)
100	5	3,520	1	1
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

3. Monitoring Frequency

In accordance with the USP <797>, a critical area must prove to meet ISO 5 classification at least once per six-month period. The same interval is also found in the ISO14644-2 guide. The frequency of determining the cleanliness class of the supporting areas is also at least once per six months as recommended by the USP. This interval is defined in the ISO14644-2 as being at least every twelve months, so the expectations of the USP are higher than that of a typical ISO 8 clean room.

Because the FDA has a more risk-based approach to monitoring, a sample every “n” months is insufficient to determine if a specific batch of product was manufactured to specification and quality-defined attributes.

We recommend that measurements to confirm air cleanliness in critical areas be taken at sites where there is most potential risk to the exposed sterilized product, containers, and closures. The particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample. Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters.²

Therefore, environmental monitoring should be performed during those periods when product is being exposed to the ambient environment, and records should show that a level of control was present during these periods. The FDA sets no recommendations for the supporting areas; however, the Parenteral Drug Association (PDA) recommends that they be sampled at least once per week for ISO 7 and at least once per month for ISO 8 (PDA Journal of Pharmaceutical Science and Technology, Volume 57 No.2 March/April 2003).

For more information on particle monitoring in pharmaceutical environments, read Particle Measuring Systems Application Note, “Particle Monitoring Requirements in Pharmaceutical Cleanrooms.”

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Acknowledgements

1 USP. *United States Pharmacopoeia General Chapter <797> Pharmaceutical Compounding – Sterile Preparations.*

2 FDA. *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice.* September 2004.

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