

Human Cell, Tissue, and Cellular and Tissue-Based Products (HCT/P) Environmental Monitoring Requirements

The Food and Drug Administration (FDA) requires human cell, tissue, and cellular and tissue-based product establishments to follow the current Good Tissue Practice (GTP), which governs the methods used in, and the facilities and controls used for, the manufacture of human tissue and cellular and tissue-based products. The following regulation is to be enforced as of May 25, 2005:

21 CFR 1271—Human Cells, Tissues, and Cellular and Tissue-Based Products

21 CFR 1271.195 Environmental control and monitoring

Section 1271 requires facilities to establish and maintain procedures to adequately control and monitor environmental conditions and to provide proper conditions for operations. The regulations were created to improve protection of the public health. Section 1271.195 specifies the monitoring parameters required. The excerpt from the regulation is below.

a. *Environmental control.* Where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, you must adequately control environmental conditions and provide proper conditions for operations. Where appropriate, you must provide for the following control activities or systems:

- (1) Temperature and humidity controls;
- (2) Ventilation and air filtration;
- (3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and
- (4) Maintenance of equipment used to control conditions necessary for aseptic processing operations.

b. *Inspections.* You must inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly. You must take appropriate corrective action as necessary.

- c. *Environmental monitoring.* You must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents. Where appropriate, you must provide environmental monitoring for microorganisms.
- d. *Records.* You must document, and maintain records of, environmental control and monitoring activities.

Lasair III Portable Particle Counter and MiniCapt Portable Microbial Sampler for 21 CFR 1271 Monitoring

Lasair III 5100



Minicapt 100



The primary purpose behind these requirements is to prevent the contamination of tissues or tissue/cellular products. The regulations specify that the ventilation and air filtration system requires monitoring. Standard monitoring procedures include particle counting and air velocity monitoring within the clean zone and differential pressure monitoring between adjacent areas. Monitoring proves control over products directly exposed to the air quality of the clean zone, and it also protects adjacent rooms from cross-contamination.

In addition to particle counting, Section 1271.195c also mandates that monitoring for microorganisms should be done when appropriate. The FDA clarifies their expectations in the Federal Register, Vol. 69, Part IV (page 68629):

Conditions may differ from facility to facility (and even from room to room within a facility), with common microorganisms found in one area but not another. Each establishment should determine the microorganisms that may exist in its facilities and design its monitoring program accordingly. FDA has issued a draft guidance document entitled "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing, Current Good Manufacturing Practice," dated August 2003, that may provide useful information to an HCT/P establishment that is developing procedures on environmental control and monitoring. Information on environmental monitoring may also be found in the U.S. Pharmacopoeia.

The *Guidance for Industry* was since revised and made into a September 2004 release. That release states that in critical areas, a room particulate classification of < 3,520 particles/m³ at 0.5 µm (ISO14644-1 Class 5) must be maintained, and the

supporting clean areas must be ISO 14644-1 class 6, 7, or 8, based upon a risk analysis of operations. The following table outlines ISO classifications for particles and recommended action levels for microbiological quality.

It is expected that for sterile activities (ISO Class 5), data be produced that supports the sterile products guidelines. For those products that are not sterile, sufficient proof of environmental control must be demonstrated so that contamination of products is not an issue.

Reporting Frequencies

The monitoring frequency of environmental conditions is not specifically outlined in the HCT/P regulations; clean zones should be monitored at intervals based upon risk of contamination. For critical areas, a portable particle counter (e.g., Lasair III-310C) and an active air microbial sampler (e.g., MiniCapt) should be used at least once per shift, and the supporting areas should be monitored with the particle counter and microbial sampler at least once per day. Areas immediately surrounding the laminar flow area (critical zone) should be monitored once per week, and once per month for areas of lesser risk.

Clean Area Classification ^a (0.5 µm Counts/ft ³)	ISO 14644-1 Designation ^b	ISO 14644-1 (0.5 µm Counts/m ³)	Microbiological Active Air Action Levels ^c (cfu/m ³)	Microbiological Settling Plates Action Levels ^{c,d} (90 mm diameter, cfu/4 hours)
100	5	3,520	1 ^e	1 ^e
1,000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

- a) All classifications are based on data measured in the vicinity of exposed materials/articles during periods of activity.
- b) ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
- c) Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
- d) The additional use of settling plates is optional.
- e) Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

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