Application Note

Particle Monitoring Requirements in Pharmaceutical Cleanrooms

Why do I need a Particle Counter?

This is a frequently asked question from current or potential pharmaceutical cleanroom personnel. The legislation and cGMP guidelines clearly state why microbiological monitoring must be performed and impose limitations for production environments. Little mention is made of routinely monitoring the particle count levels. So what value does it add and why should I be doing it?

All drugs must be manufactured in accordance with the current Good Manufacturing Practice (cGMP) regulations. In the United States these regulations are governed by the Food and Drug Administration (FDA) as the 21st Code of Federal Register. The pharmaceutical company manufacturing the product must therefore prove that they have been in compliance with the regulations at every stage before a drug can be released to market and ultimately the end users.

The cGMP regulations govern various activities of the drugs manufacture including:

- Organization and Personnel [21 CFR 211 Subpart B]
- Buildings and Facilities [21 CFR 211 Subpart C]
- Production and Process Controls [21 CFR 211 Subpart F]

The pharmaceutical company must have a quality control department that has the responsibility for drug approval independent of the production department. This department is responsible for the routine quality assurances that:

Establishes documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes'

FDA definition, in 'General Principles of Validation' [May 1987]

To satisfy the assurances required, the products are manufactured in a controlled environment. Cleanrooms are employed to reduce the variability of potential production environments and as controlled environments can be regulated to meet specific standards. GMP regulations require that these environments are rigorously monitored to ensure that there is full and constant awareness of current environmental conditions, both for viable and non-viable contamination.

What is a Cleanroom?

A cleanroom is the fundamental starting point for contamination control. In Federal Standard 209 (FS209E), a cleanroom is defined as a room in which air filtration, air distribution, utilities, materials of construction, and equipment are maintained in a controlled manner. Operational procedures are defined and regulated for airborne particle concentrations to meet appropriate particulate cleanliness classifications. ISO/TC209 14644-1 is the international standard of defining cleanroom contamination levels.

Pharmaceutical cleanrooms are classified according to the particle concentration of the air required to meet the cleanliness criteria for the manufacturing process being performed. Using the ISO standards the lower the classification number, the lower the particle concentration. Originally cleanrooms were classified according to the number of particles per cubic foot at 0.5µm. The determination of the cleanroom class is a process based on actual statistically valid measurements, as described below.

Particle Count Room Classification

There are three measurements phases involving particle counting in as-built rooms:

- As built, a completed room with all services connected and functional, but without production equipment or personnel within the facility.
- At Rest, a condition where all the services are connected, all the equipment is installed and operating to an agreed manner, but no personnel are present.
- Operational, All equipment is installed and is functioning to an agreed format, and a specified number of

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personnel are present working to an agreed procedure.

The airborne particle count test is performed by determining particle counts at defined grid locations within the as-built room. The test points should be regularly spaced throughout the room to permit the definition of the air cleanliness as it approaches the work area. If equipment location requires modification of the uniform grid pattern, then this situation should be reported.

The number of measurements taken at each test point depends on the cleanroom class and the statistical requirements specified in the standards. The standards also state that the data should permit defining the classification level with 95% confidence level. It is recommended that a particle counter capable of 0.5µm sensitivity be used for the definition of classes = 100 (ISO class 5).

To calculate the:

Minimum number of sample points required: Area $(m^2)^{0.5}$

Minimum sample volume is determined by: $\frac{20}{\text{Class Limit}} \times 1000$

Total required sample time (minutes):

$$\frac{\text{Minimum volume}}{28.3} \times \text{minimum No samples}$$

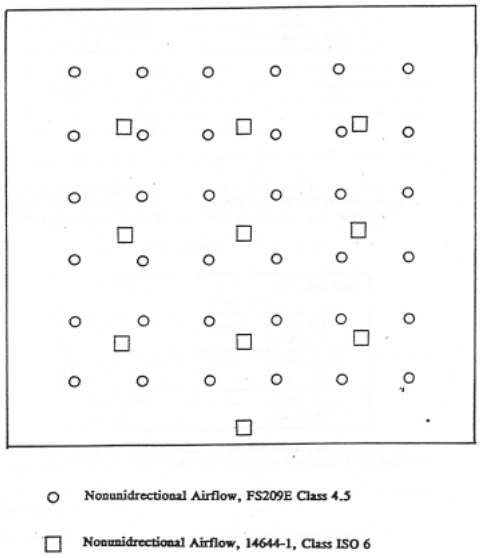
The following table shows the latest cleanroom classifications. Note that ISO Class 4 is equivalent to 209 Class 10.

Classification Numbers (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below					
	0.1µm	0.2µm	0.3µm	0.5µm	1µm	5.0µm
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1 000	237	102	35	8	
ISO 4	10 000	2 370	1 020	352	83	
ISO 5	100 000	23 700	10 200	3 520	832	29
ISO 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO 7				352 000	83 200	2 930
ISO 8				3 520 000	832 000	29 300
ISO 9				35 200 000	8 320 000	293

Pharmaceutical Cleanroom Utilization

We can therefore prove that a cleanroom meets a prerequisite standard using a particle counter. The room classification achieved also dictates the production activities, which can be performed in the cleanroom. A document produced by the FDA and published in 1987 defines two areas. A 'critical area' where the sterilized dosage form, containers, and closures are exposed to the environment and a 'controlled area' where unsterilized product, in-process materials, and container/closures are prepared. The environmental requirements for these two areas given in the Guide are as follows:

Critical areas. 'Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations is of acceptable particulate quality when it has a per-cubic-foot particle count of no more than 100 in a size range of 0.5 micron and larger (ISO Class 5). The sample values are determined when measured not more than one foot away (300mm) from the work site, and upstream of the air flow,



during filling/closing operations. The agency recognizes that some powder filling operations may generate high levels of powder particulates, which, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the one foot distance and still differentiate "background noise" levels of powder particles from air contaminants which can impeach product quality. In these instances, it is nonetheless important to sample the air in a manner, which, to the extent possible, characterizes the true level of extrinsic particulate contamination to which the product is exposed.

Air in critical areas should be supplied at the point of use as HEPA filtered laminar flow air, having a velocity sufficient

to sweep particulate matter away from the filling/closing area. Normally, a velocity of 90 feet per minute, plus or minus 20%, is adequate, although higher velocities may be needed where the operations generate high levels of particulates or where equipment configuration disrupts laminar flow.

Air should also be of a high microbial quality. An incidence of no more than one colony forming unit per 10 cubic feet is considered as attainable and desirable. Critical areas should have a positive pressure differential relative to adjacent less clean areas; a pressure differential of 0.05 inch of water (12.5Pa) is acceptable'.

Controlled areas. 'Air in controlled areas is generally of acceptable particulate quality if it has a per-cubic-foot particle count of not more than 100,000 in a size range of 0.5 micron and larger (ISO Class 8) when measured in the vicinity of the exposed articles during periods of activity. With regard to microbial quality, an incidence of no more than 25 colony forming units per 10 cubic feet is acceptable.

In order to maintain air quality in controlled areas, it is important to achieve a sufficient air flow and a positive pressure differential relative to adjacent uncontrolled areas. In this regard, an air flow sufficient to achieve at least 20 air changes per hour and, in general, a pressure differential of at least 0.05 inch of water (with all doors closed), are acceptable. When doors are open, outward airflow should be sufficient to minimize ingress of contamination'.

(Guidelines on Sterile Drug Products Produced by Aseptic Processing, CDER, FDA 1987)

Environmental Monitoring

To meet the FDA compliance an area has to be proven to be within specification to the standards to be used for drug manufacture. These clean manufacturing environments need to be rigorously monitored to ensure that there is a full and constant awareness of current conditions, including the detection of periodic events which could be catastrophic if gone unnoticed. Constant monitoring creates a constant flow of information, which results in large volumes of data being accumulated.

The manufacturing facility should therefore have a comprehensive environmental monitoring program, which includes monitoring for non-viable and viable air-borne particulates, surface viable contamination and, in the aseptic areas, personnel [21 CFR 211.42]. These procedures should address frequencies and locations for the monitoring sample points, warning and alarm limits for each area, and corrective actions, which need to be undertaken should any of the areas show a deviation from expected results. Actions taken when limits are exceeded should include investigation into the source of the problem, the potential impact on the product, and any measures required preventing a recurrence.

Generally, less frequent monitoring is required in areas of a lower classification i.e. ISO Class 8 or unclassified areas. This reduced frequency monitoring performed in "controlled" environments (ones with some level of particulate controls) should be of the same integrity as that sampled in the highest classification.

Room Classification	Maximum concentration limits (particles/m^3 of air) for particles/ Airborne Viables (cfu/m^3)		
	0.5μm	5.0μm	Viable cfu/m^3
A-Operational	3,500	0	<1 /90mm settle plate <1 /4 hrs
B-Dynamic	350,000	2,000	<10 /90mm settle plate <5 /4 hrs
C	3,500,000	20,000	<100 /90mm settle plate <50 /4 hrs
D	Not Defined	Not Defined	<200 /90mm settle plate <100 /4 hrs

During a quality, or regulatory, audit the specifications for viable and non-viable particulates will be reviewed. Focus is placed on the viable monitoring, as this potentially will have a greater impact on the final product. Rooms are however classified for both, with the levels of viable particulates being a function of the room classification, determined by non-viable monitoring.

AIRBORNE CLEANLINESS CLASSES

The data is for EU based cleanrooms

Manufacturers have to determine that ISO Class 5 conditions have been validated and are maintained in areas in which sterile product and components, including container/closure systems, are exposed. Ensure that if limits are exceeded, an investigation is conducted and appropriate action is taken. Perform microbial identification, especially in aseptic areas and see if any trends are apparent.

The PMS Solution to Monitoring Particulate levels in Aseptic Cleanrooms

A compact approach is to build a disk drive into the portable particle counter itself. The data can then be exported to a computer for statistical manipulation as required. This raises current issues that data, which is inherently editable, does not comply with the FDA 21-CFR-part-11 ruling, defining the security of electronic records and signatures. There is an increasing need to monitor more locations more regularly than can be easily achieved using a single mobile counter. This need is being driven by the desire to reduce operational costs, to increase confidence in good manufacturing practices and fulfil regulatory requirements.

One way of achieving the monitoring levels required is to install a Facility Monitoring System, which includes particle counters. A Facility Monitoring System is either a single continuous particle counter installed into a critical location, or an arrangement of instruments suitable for making the measurements required, these are linked to a central monitoring computer. The computer controls the intake of data from the particle counters and logs and displays the information, reporting to the operator any changes in conditions or trends.

Inputs to the Facility Monitoring System may be from sources other than particle counters. This leads to a full independent environmental monitoring system into which data from viable monitoring can be added, along with data from differential pressure sensors, air velocity and temperature / relative humidity sensors as required.

Such automated, computer controlled Facility Monitoring Systems will provide increased vigilance while also decreasing the labor requirements to make measurements, manually transfer data to interpretive applications, and produce reports to support product release. The new ISO 14644-2 regulations also allows that a cleanroom with an installed particle monitoring system (continuously measuring the particulate levels) requires the revalidation of a class 5 (class 100) area to be repeated every 24 months rather than the 6 months should a system not be present.

If the system is well planned, a fast detection of potential problems in operating conditions will occur enabling counter measures to be taken rapidly. Long term any significant trends in operating conditions can be monitored and statistical analysis of data should allow for closer control and identification of normal and abnormal conditions.

There are three basic approaches to obtaining automated particle counts:

- Multiple tubes via multi-port scanning manifold linked to a particle counter.
- Individual particle sensors.
- Combination of manifolds and particle sensors.

Multiple Tubes- scanning manifold systems are very common and consist of a central manifold with up to 32-sample tubes radiating from this central location. Each tube is capable of drawing a sample a distance of 38m (125ft) from the manifold to a single particle counter. The advantages of such a system are:

- Low cost per sample point monitored. The system requires a particle counter, aerosol manifold and lengths of flexible tubing for the number of positions monitored.
- Low maintenance and calibration costs. Only a single instrument per manifold to calibrate and service.

Disadvantages of manifold based systems:

- Can only sample one location at a time and transient events may be missed. However, sample sequencing may be biased to monitor the most critical locations more often.
- Loss of particles of 5 micron and greater in the tubes due to sedimentation and impaction may occur. However a properly designed system that maintains turbulent flow in the tubes, eliminates unnecessary valves and minimizes sharp bends in the tubing will provide good results.

Increasingly to ensure that ‘continuous’ monitoring is being preserved, the use of dedicated locally mounted sensors to sample the environment is being used. The particle sensor consists of a small enclosure housing an optical system, a light source (laser diode) and signal generation electronics. The sensors often require an external vacuum source and signal communication cable to transmit data to the central monitoring computer. The advantages of such a system are:

- The sensors monitor continuously and report data to system, therefore detecting short lived particle burst situations.
- Simple and low cost installation.
- Ease of relocation to alternative positions.
- Provides highest level of confidence.

Disadvantages of independent sensor systems are:

- Higher cost per point sampled, each sampling point requires an individual sensor.
- Higher cost of ownership. Each sensor will require calibration and service.

An alternative to either of the systems is one, which utilizes the advantages of both systems. The majority of sampling being monitored with one (or more) manifolds and specific critical locations continuously sampled by individual sensors.

The data is reported back to a central monitoring software package. The software is a validated package, which reports the data to the users in multiple formats. These formats include real-time current values, spreadsheet viewing of historical data and live time plots. This data which is saved to the hard drive must comply with the FDA 21-CFR-part-11 ruling, and is encrypted onto the database, with security and audit trail capabilities. The system must also be able to report problems to field operators a system of local alarm devices; paging and Email annunciation of out of condition warnings and alarms is employed.

Legislative Warnings

The warning letters below are cases over the past four years, which identify either a problem where a manufacturer cannot produce environmental data to prove control over conditions, or has not reacted to out of specification alarms produced by the system.

February 1997

PARTICULATE MONITORING. The commitment to review a specific process and identify stages of transient high particle counts cited in FD483 observation num. 7 and establish subsequent operating limits, fails to address the problem of counts outside of established limits. Your description of the high counts as "transient" (i.e., lasting only a short time) does not correct the deficiency, nor will the commitment to establish new operating limits. The approach should be to identify the cause and modify or correct the situation causing the high counts so that the already established action limit can be met. We are also concerned that this was not corrected by your QC unit before FDA arrival.

January 1998

Failure to assure an adequate system for monitoring environmental conditions [21CFR211 .42 (c)(lo)(iv)] in that smoke studies to demonstrate unidirectional airflow have not been conducted for filling lines XX.

May 1999

Critical surfaces for the aseptic core are not maintained in a Class 100 (ISO class 5) environment between equipment sterilisation and filling operations. Our inspection noted that there is no assurance that critical surfaces in the aseptic core, such as, their XXXXXX are maintained under a Class 100 (ISO class 5) environment between sterilisation of the equipment and filling operations.

December 1999

The quality control unit did not assure that adequate systems and controls were in place to monitor the functioning of and to detect malfunctions of the air handling systems used to control and assure aseptic conditions in aseptic manufacturing areas.

The quality control unit did not assure that all areas used for aseptic manufacturing and processing operations are appropriately controlled and classified for their intended use.

June 2000

Your quality unit released batch of XXXXX cc vials that failed specifications for the presence of particulate. The quality unit concluded that the particulate were present only in the end-of-fill portion of the batch and released the portion of the batch believed to be unaffected by the presence of particulate. However, this conclusion is not supported by any investigation to show that foreign particles were only introduced at the end of the fill.

January 2001

Failure to establish an adequate system for monitoring environmental conditions of aseptic processing areas [21 CFR 211 .42(c)(10)(iv) and 600.11(a)] in that there are no }conditions are maintained in the plastic curtained "class — data that class —. area adjacent to the filling station outside of the class — area during connection of the bulk tank to the filling line. In addition, there is no environmental monitoring in the area during the connection.

Source of information is from www.fda.gov/foi/warning.htm

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