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ENVIRONMENTAL MONITORING OF VIABLE AND NON-VIABLE PARTICLES IN PHARMACEUTICAL INDUSTRY: A REVIEW

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ABSTRACT

This article describes a review of environmental data for clean rooms in the pharmaceutical industry. To investigate the possibility of correlation between them, two parameters were compared: 1) total nonviable airborne (0.5 and 5µm) and viable particulate matter, and 2) surface contamination. The investigator found areas identified as A, B and C in the moment or state of activity that included "at rest" and "dynamic" circumstances. A cleanroom is an atmosphere usually used in industrial or scientific investigation which has lower levels of contaminants from the environment such asa airborne bacteria, dust, particles from aerosols and chemical vapours.Most specifically, a clean room has a controlled pollution level that is set at a given particle size by the number of particles per cubic metre. The work space is sensitive to airborne pollution, which is why adequate protection from contaminants entry must be provided. However, the manufacturing development itself produces gases that need to be removed from the factory in order to avoid contamination in areas where processing takes place.The required classifications for clean air, air handling unit, and its various apparatuses are discussed in this document.The control of airborne particulate matter is required as part of good industrial practice.

INTRODUCTION

Environmental monitoring is a system intended to establish regulation of viable (living micro-organisms) and non-viable particulate matter in classified areas. Such areas contain product fill /finish cleanrooms, laminar flow hoods,formulation tank rooms, biological safety hoods and insulators, glove packets, moulding machines, package assemblage lines, sterile packaging and Intravenous (IV) compounding areas. (Fig:1).

Fig: 1

Viable control refers to checking for the bacteria, yeast, and mold identification and enumeration. It induces monitoring of surfaces of staff, air and area used for microbial contamination, non-viable monitoring of the atmosphere which be located guideline for particle counts determined through laser counter. Organizations who take their cleanroom services tracked to ensure they are meeting their required / desired quality standards. The areas which are experimented in a cleanroom of a manufacturer embrace.

Viable Particle Monitoring: Biological monitoring of the ecosystem includes the gathering of data about the number of micro-organisms collected from soils, soil and humans. Non-viable particle including, a physical check is also contained within the system because of this task has always remained with the branch of microbiology to complete and because of the theoretical relationship between large numbers of viable counts and nonviable particles. The feasible count component of environmental monitoring is to list the quantity of micro-organisms contemporary in a cleanroom by using the following types:

1. Airborne Monitoring:
   - ❖ Active air: Vo1umetric Air Sampler sampling.
   - ❖ Passive sampling of air: settle down plates

Surface Monitoring
   - ❖ Sample surface: contact plates
   - ❖ Sample surface: Swabs

Personal Monitoring
   - ❖ Plates of sleeves/gowns.
   - ❖ Finger plates

Viable monitoring limits:

Grade	Air Sample cfu/m³	Settle Plates (∅ 90 mm), cfu/4 hours	Contact Plates (∅ 55 mm), cfu/plate	Glove Print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Non-Viable Particle Monitoring

A Non-viable monitoring particle is an object which does not cover living micro-organisms but functions as per viable particle transport. Particles which are not viable are monitored using the particle counter in Fig 2.

Fig: 2

Particle counters Principle: The use of particulate counters that do not differentiate between the viable and nonviable particles. However, stand much technically innovative than air samplers to monitor nonviable particles. The United State has established particle counters. In the 1960s the army was used in the aerospace industry and later evolved for usage in the semiconductor & pharmaceutical industries. They comprise a dark chamber / sensor with a concealed laser that usage mirrors and optics to display the particles and pump for sample draw needed by the instrument. The key idea behind particle recognition and dimensioning is easy, that vacuum pump absorbs the sensor and laser beam of the object. At this point, it converts the 1ight from the 1aser through a mirror based on the photo detector and turns this reproduced light into an electric beat via the photo detector. The signals are weighed and weighted in the particle counter by the electronics. The larger the object, the smaller the photo detector, the larger the electrical pulse in Fig: 3. [1]

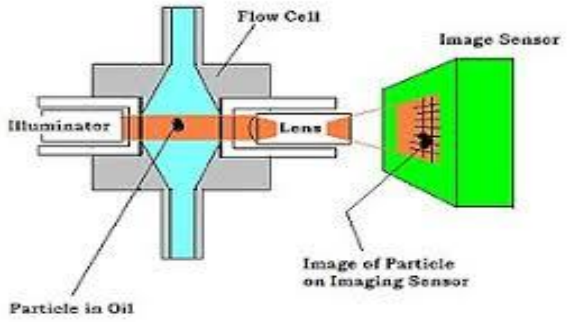

Fig: 3

Environmental monitoring is a main aspect of pharmaceutical production regulation and quality controller. During drug production the manufacturing environment has to be regulated and monitored. Finished drug products have to be safe and contamination-free. The two approaches taken to produce sterile drugs are terminal sterilization and aseptic manufacturing. Terminal sterilization is the mechanism by which products and containers are sterilized, made with the material in its containers and the product in its final form. The individual components are sterilized separately in aseptic filling or packing, and brought together in the final form in a sterile environment. Sterile medicinal products should only be produced by aseptic processing if terminal sterilization is not feasible.

Viable microorganisms are the biggest concern with producing sterile medicines. It is not possible to track these in real time with current technology particle counters play an essential part in assessing air quality during sterile processing.[2]

Cleanrooms and Particle Counting:

Manufacturing of sterile pharmaceuticals takes place in different cleanroom grades. This is the most critical phase during aseptic planning and filling. During the manufacture of these medications, particle counting, microbiological control, temperature, relative humidity, and pressure differential measurements must be controlled.

Standards for Cleanrooms:

Cleanrooms are defined by the maximum allowable amount of particles per unit volume of air. Usually used volumes are cubic meters (m^3), and cubic feet (ft^3).

Cleanroom requirements also define:

• Minimum sampling volume (20 particles) to collect statistically valid trials

• Minimum amount of points to identify a region based on numerical criteria.

Components of an environmental Monitoring system includes:

• Monitoring of Non-viable and airborne particulate

• Monitoring viable surface contaminant

• Airborne, safe contaminant monitoring

•Control of humidity and temperature

• Monitoring of differential pressure.[2]

Standards GeneralPharmaceutical Regulatory/ Guidance Documents

- FS 209E -United State Federal Standard 209E
- ISO -International Standard of Organization –the “NEW” standards
- USP -United States Pharmacopeia
- IEST-1nstitute of Environmental Sciences and Testing
- EU -European Union GMP’s
- FDA Aseptic Guidelines [3]

A robust suite for the observing of viable & non-viable particles through the assembling of pharmaceutical measurement structures ought to be well-characterized and practical for the

duration of the existing pattern of the item. This is particularly valid for aseptic handling activities, as a powerful ecological checking system can give significant data about the nature of basic assembling zones and subordinate clean territories. Moreover, the natural observing project should give interpretable information that can help with recognizing genuine or potential sullying issues related to explicit hardware, parts, forms, as well as operational exercises. From an assembling control point of view, ecological checking information ought to be fit for identifying an antagonistic float in natural conditions in a convenient way that would take into consideration important and compelling restorative activities to be attempted.[4] Environmental monitoring systems usually consist of two elements that analyse viable particles (i.e., microorganisms) and non-viable ones. The U.S. Food and Drug Administration (FDA) Regulation for Industry: Sterile Drugs Developed by Aseptic Processing-Current Good Manufacturing Practice (cGMP) and the European Commission (EU) Guidelines Good Manufacturing Practice, Manufacture of Sterile Medicinal Products (EU) are books providing route for the observing of viable and nonviable particles in sterile processing clean areas in Table I and II.

Pharmaceutical product development is anextremely controlled method, whether the finish product is sterile, terminally treated, lyophilized or even a bulk ingredient from it. The conditions in which the manufacturing activities are carried out must therefore be regulated and proven to be managed by monitoring. Filters and the clean rooms or limited work stations they provide are the tools for handling pollutants in the industrial environments.HEPA filters are used to purify a cleanroom's air supply. There are 3 specific kinds of clean rooms used in pharmaceutical consumption:

1. Modernwith turbulent movement air distributed at an optimal rate to diluted particle absorption in a region to a suitable limit.
2. Unidirectional spray, with the air velocity to remove debris from critical areas as a shower.
3. A blend of both technologies.[5]

Airborne particulate matter, an air quality measure, can be categorized as viable or non-viable pollutants and may come from humans or manufacturing areas. Such pollutants have had adverse effects on the wellbeing of patients (9–12), supporting the need to control concentrations of airborne particulates. [6]

Contamination ControlKey Elements:

To get an improved idea of the complete image of pollution management we should look at many areas of concern. These are the things to consider when delivering an actual contamination controller program.

- **High Efficiency Particulate Air Filter (HEPA)-** Such filters are particularly significant in keeping track of contaminants. They filter particles with a minimum particle-combined efficiency of 99.97% as small as 0.3 microns.
- **C1eanroom Architecture-**Cleanrooms are planned to complete and maintain an airflow in which all the body of air moves along parallel flow lines in a confined area with uniform speed. This movement of air is known as a laminar flow. The more airflow controls the more turbulence. The turbulence can affect motion of the particles.
- **Filtration-** Including the widely used HEPA filters in cleanrooms, a variety of further filtration systems are used to extract particles from liquids gases. Those filters are necessary for actual control of contamination.

Cleaning: Cleaning is a key component in preventing pollution. Conclusions regarding the cleanroom conservation and cleaning specifics need to be made. Cleanroom management and contractors must write down and decide on the applications and procedures.

Cleanroom Garments: Cleanroom confectionery standards can vary from area to area.It is critical to understand the cleanroom management specifications for the local clothing.In almost every cleanroom setting, face masks, head-covers and gloves are normal. Smocks are becoming increasingly popular. In very clean environments, jump suits are needed.

Humans in cleanrooms: When humans are in cleanrooms, there are both psychological andphysical issues. Physicalactions such as swift movement and horseplay can rise the

contamination.Psychological issues such as humidity, room temperature claustrophobia, attitude and odours towards the workplace are significant. Below are a few types in which people create contamination:

1. Re-forming processes of the body-oils, skin flakes hair and sudor's.

2. Behaviour- Movement rate, coughing and sneezing.

3. Attitude- Work practices and inter worker contact.

People are an important basis of cleanroom pollution. Consider the activities of the people recorded below. Note the number of particles emitted during those activities per minute.[7]

Materials and Methods: The analysis of the material of this work involved a viable and non-viable presence of particulates in the air in safe areas-Classes A, B, and C according to the European Guide to Good Manufacturing Practices as well as viable surface-settled particles in the regions.[9]

Cleanroom Classification for Pharmaceutical industry [8, 14]

The cleanroom classification according to Federal 209D and ISO Standards is given in Table No.1.

The system was part of an environmental control plan, and was started immediately after completion of the facility's construction phases. The procedure was either in compliance with the Institute of Environmental Sciences and Technology Controlled Pollution Division's advice in the "at rest" and "in operation" cleanroom situation or "dynamic."

The environmental control process includes higher number of activities in the "at rest" period, including the certification of the rooms. Such certification consisted of producing documentary evidence on the suitability of air conditioning, as well as the method of washing, asepsis, and gowning, among others, to ensure a suitable environment for the manufacture of sterile items. The complex process included full room management, integrating the planned operational activities.

In the analysis of the data collected the description of each room was not preserved. The class to which each sampling point belonged has however always been valued. [9]

Cleanrooms[10, 11]:

A room where airborne particle concentration is controlled and created and used to reduce the absorption, generation and maintenance of particles in the room and other related parameter for example, temperature, pressure and humidity shall be regulated where appropriate.

1. The State "at rest" remains the situation in which the setting up is whole with apparatus installed and working in a manner decided through the purchaser and manufacturer, but without any personnel present.
2. The state of "in operation" is the situation i n which the insta1lation operates in the giv en working mode and the required number of staffs is present. The areas and their rela ted environmental controller system should be considered to achieve the states of "rest ing" as well as "in operation".

Critical area (Grade A)

- The critica1 area is manufacturing area in which the sterilized goods and resources a nd their outsides are exposed straight to th e atmosphere.
- The particle content per cubic meter of 0. 5μm in diameter in the critical area must b e monitored in both operating and non-operating conditions to be below 3.520.
- The count of micro-organisms and airborne particles should be routinely tracked at locations which are vital to the sterility of pharmaceutical products by correct procedure.

Direct support area (Grade B)

Direct support area is described as a critical are a context where aseptic dispensation is perform ed using an exposed clean booth or a restricted contact barrier system.Direct support area is a work environment for workers operating machines built in the critical area and that supervising machine operation. The number of particles (diameter: 0.5μm) per cubic meter in the direct support area should be managed under operating and non-operating conditions

below 352,000 and 3,520, respectively. Pursuant to domestic and international air quality requirements, these air cleanliness levels are known as Grade B, Class 10,000, or ISO-7.

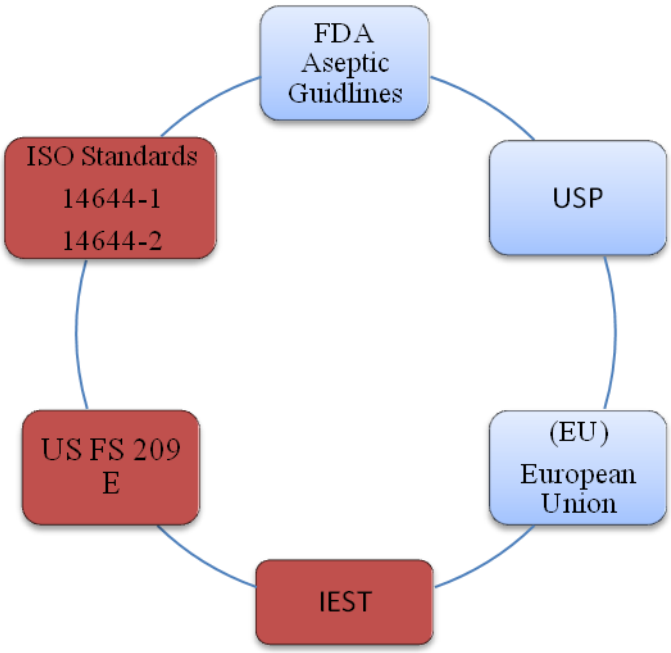

Fig: 1 Cleanroom Standards

Table I- FDA Air Classifications[5, 12]

1SO Designation	**C1ean Area C1assification**	**≥0.5 µm Particles/m³**	**Microbiological Active Air Action Levels [c](cfu/m³)**
5	100	3520	1[c]
6	1000	35200	7
7	10000	352000	10
8	100000	3520000	100

Table II- EU Air Classification[5,13]

EU Grade	Maximum permitted number of particles per cubic meter equal to or greater than the tabulated Size				Recommended Limits for Microbial Contamination during Operation*al*—Air Sample (cfu/m³)
	At Rest		At Operation		
	≥0.5µm Particles/m³	≥5.0 µm Particles/m³	≥0.5 µm Particles/m³	≥5.0 µm Particles/m³	
A	3520	20	3520	20	<1
B	3520	29	352000	2900	10
C	352000	2900	3520000	29000	100
D	3520000	29000	Not defined	Not defined	200

Peop1e Activity	**Partic1es/Minute (0.3 microns and larger)**
Motionless (Standing or Seated)	100,000
Walking about 2 mph	5,000,000
Walking about 3.5 mph	7,000,000
Walking about 5 mph	10,000,000
Horseplay	100,000,000

Table 1: Standards for Cleanroom as per ISO 14644-1 and FED STD 209E

Class	Maximum particle/ft^2					ISO Equivalent
	≥0.1 µm	≥0.2 µm	≥0.30 µm	≥0.5 µm	≥5 µm	
1	35	7.5	3	1	0.007	ISO 3
10	350	75	30	10	0.07	ISO 4
100	3500	750	300	100	0.7	ISO 5
1000	35000	7500	3000	1000	7	ISO 6
10000	35×10^4	75×10^3	30×10^4	10×10^4	70	ISO 7
100000	35×10^5	75×10^4	30×10^5	10×10^5	700	ISO 8

Table 2: Classification based on airborne particulates. (WHO requirements)

	Maximum permitted number of particles per m^3 greater than or equal to the tabulated size			
	At rest [a]		In Operation [b]	
Grade	0.5µm	5.0µm	0.5µm	5.0µm
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined	Not defined

Indirect support areas (Grade C or D)

It is used for handling materials and goods before sterilization methods; for example, indirect support areas include a pre-sterilization drug solution storage area and a washing and cleaning area for sterilization equipment and appliances. Indirect support area air cleanliness may be also of the following 2 Grades. One grade state that, under operating and nonoperating conditions, the particle content per cubic meter (diameter: average 0.5µm) should not exceed 3,520,000 and 352,000, respectively. In accordance with domestic and international air quality requirements, these levels of cleanliness are known as grade c, class 100,000, or ISO-8 (standard under operating conditions). The other classification states that the volume of Particles per cubic meter (diameter: 0.5µm) under non-operating conditions should not exceed 3,520,000. This level of cleanliness is called Grade D. [10, 11]

CONCLUSION:

A clean facility is important to meet today's and tomorrow's analytical challenges. Steps will be taken to set up trace element and radionuclide detection and testing equipment. Because man's mindset and knowledge of recent advances are key in preserving and using safe facilities, continuing education and training of laboratory personnel is very necessary to promote further advancement. As a consultant engineer focused on clean room technologies, we see several small units closing down due to the shortage of accessible clean room equipment. It takes an hour to switch from the existing production system to the manufacturing system in accordance with the mandatory requirements for developing low-cost clean room. This inspired us to experiment with the creation of a device using widely accessible duct able divisions.

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