HVAC Area Classification

By – www.pharmatechinfo.com

PHARMACEUTICAL AREA CLASSIFICATION

AGENDA

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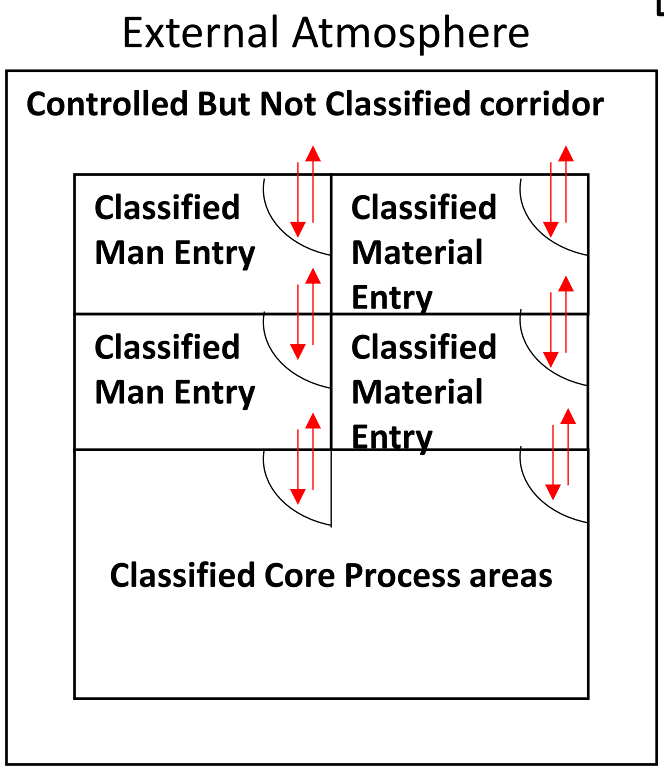
OBJECTIVE

In pharmaceutical industry, classification of process areas is crucial to ensure the safety and quality of pharmaceutical products. This classification is based on the level of environmental control required to minimize the risk of contamination from airborne particles and micro-organisms.

Primary objective of pharmaceutical process area classification is to establish controlled environments that meet the specific requirements of the manufacturing process. this classification helps to:

- *Minimize the risk of product contamination*
- *Maintain product quality*
- *Ensure patient safety*



Example of Higher classified area protected by multiple levels of lower classified and controlled areas

AREA CLASSIFICATIONS

ISO 14644 CLASSIFICATION FOR MAXIMUM PARTICLE /m3						
ISO 14644-1:2015 Cleanroom Standard – This chart details for each classification the maximum number of particles in micrometers (µm) permitted per cubic meter of air.						
Class	Maximum Particles per m3					
	≥0.1 µm	≥0.2 µm	≥0.3 µm	≥0.5 µm	≥1 µm	≥5 µm
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	1,00,000	23,700	10,200	3,520	832	29
ISO 6	10,00,000	2,37,000	1,02,000	35,200	83,200	2,930
ISO 7				3,52,000	8,32,000	2,930
ISO 8				35,20,000	8,32,000	29,300
ISO 9				3,52,00,000	83,20,000	2,93,000

AREA CLASSIFICATIONS

CLASSIFICATION WITH RESPECT TO GMP CATEGORISATION						
			Maximum Permitted Number of Particles/m3			
			At Rest		In Operation	
GMP Grade	ISO 14644-1 Standard Classification	FED STD 209E Classification (0.5µ Particles per ft3)	≥ 0.5 µm	≥ 5.0 µm	≥ 0.5 µm	≥ 5.0 µm
A	5	100	3 520	20	3 520	20
B	6	1000	3 520	29	352 000	2 900
C	7	10000	352 000	2 900	3 520 000	29 000
D	8	100000	3 520 000	29 000	Not defined	Not defined

SCOPE

The scope of area classification in a pharmaceutical industry is both broad and deep. It involves:

- **Identifying and segregating areas:** Defining which parts of the facility require stringent environmental controls.
- **Qualification & Requalification:** Implementing and maintaining protocols (like URS, DQ, IQ, OQ, and PQ) to verify and re-establish compliance.
- **Integrating technical systems:** Designing HVAC and other engineering solutions to meet the precise environmental requirements.
- **Ensuring overall product safety:** Sustaining regulatory compliance and continuous quality improvement.

This meticulous approach ensures that all aspects of facility design and operation support the ultimate goal of delivering safe pharmaceutical products while adhering to stringent global and local regulations.

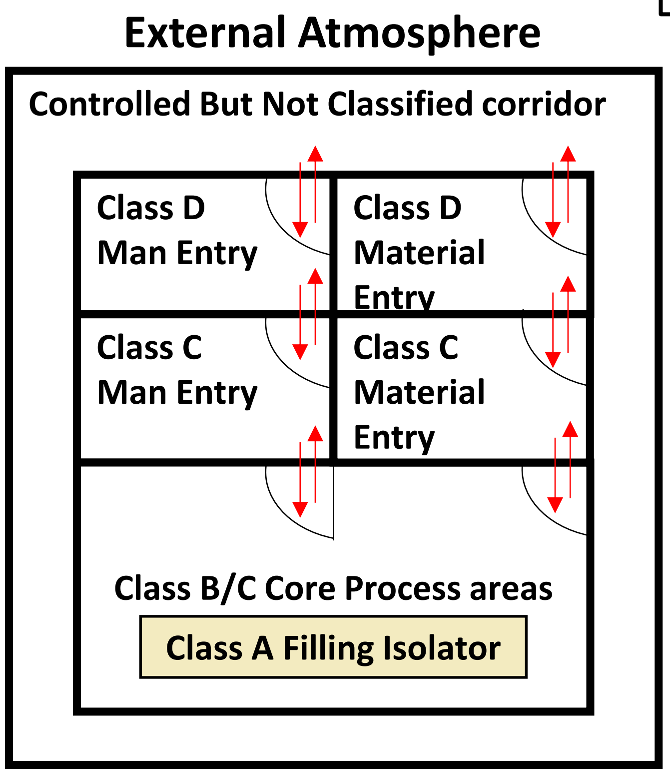
AREA CLASS & APPLICATION

All Pharmaceutical facilities are controlled facilities to protect from atmospheric contaminations. Generally It Starts with a controlled but not classified area, which shields the further classified area. Then It starts with Grade-D followed by Grade-C then Grade-B to Grade-A, as we can see in the right side Picture.

Following are the activities generally done in the specific class of the area

- **Controlled but not classified (CNC)** – Raw Material, Packing material & Finished goods are stored in this conditions
- **Grade D** – Oral Solid Dosages are generally manufactured in Grade D Conditions
- **Grade C & B** – Generally a Shielding area to Support Grade A
- **Grade A** – Sterile injectable products are manufactured in this classified area.

Note – Potent Drugs, Biological drugs, Microbial Handling, Vaccine manufacturing, Dispensing activities are also mostly follow the similar classification, but based on Product and safety requirements, some changes are possible in some specific cases.



Example of Higher classified area protected by multiple levels of lower classified and controlled areas

AREA CLASS & APPLICATION

In pharmaceutical manufacturing, process areas are segmented and classified mainly to control contamination and ensure product quality. The classification reflects both the inherent risk of a process and the controlled environmental conditions required for that operation. Here is a detailed breakdown of how this segregation works:

1. **Clean Area Grades and Their Rationale**
2. **Process Application Segregation**
3. **3. Regulatory and Design Considerations**

AREA CLASS & APPLICATION

1. **Clean Area Grades and Their Rationale**

- **Grade A:**

  This is the highest level of control, typically reserved for critical operations such as aseptic processing. In these areas—like laminar airflow workstations or isolators—the allowable airborne particulate count is extremely low (often equivalent to ISO 5 conditions during operations). Since contamination risks must be minimized at every step, these areas are designed with strict air flow, pressure differentials, and HEPA filtration systems to maintain sterility.

- **Grade B:**

  These environments generally serve as a background to Grade A zones. Although not as stringently controlled as Grade A, they still maintain high standards for cleanliness. Grade B settings support operations like aseptic filling by providing a stable background environment that minimizes the chance of contamination during critical processing.

- **Grade C and D:**

  These areas are used for less critical stages of production, such as the preparation of pre-sterile components or processes involving terminal sterilization. The controls in these zones, while still governed by Good Manufacturing Practices (GMP), allow for higher levels of particulates (often aligned with ISO 7 to ISO 9 standards) and less stringent environmental conditions compared to the aseptic areas.

AREA CLASS & APPLICATION

2. Process Application Segregation

The segregation into different grades isn't arbitrary—it's directly linked to the process application:

- **Aseptic Manufacturing Areas:**

Processes that require absolute sterility (for instance, filling sterile injections or vaccines) must be performed in Grade A environments. Here, any contamination could jeopardize patient safety, so both the immediate work area and the surrounding background (often Grade B) are rigorously controlled.

- **Non-Sterile Manufacturing or Powder Processing Areas:**

Operations like powder processing involve a less critical level of cleanliness. Still, these areas are maintained as controlled environments to prevent particulate contamination, which can affect product quality. Detailed calculations—considering airborne particle count per cubic meter, temperature, humidity, and pressure—are used to determine the required cleanliness level. Standards such as those discussed within the ISO classifications help quantify acceptable limits, ensuring that even if the conditions are less stringent than aseptic areas, they are still optimized for product integrity.

- **Transition and Buffer Zones:**

To prevent cross-contamination between areas of different grades, facilities incorporate buffer zones, airlocks, and specialized gowning areas. These transitional spaces maintain pressure differentials and use additional filtration to ensure that each process area remains within its designated environmental parameters.

AREA CLASS & APPLICATION

3. Regulatory and Design Considerations

Segregating process areas based on classification is not only a matter of operational practice—it also addresses stringent regulatory requirements. Regulatory bodies around the world (e.g., USFDA, EMA) mandate that manufacturers implement and adhere to strict environmental controls. This ensures that the levels of microbial and particulate contamination are kept to a minimum relative to the risk posed by the process. As a result:

Design elements such as HEPA filters, laminar versus turbulent airflow arrangements, pressure controls, and regular particulate monitoring are integrated into the facility's architecture.

Process validation and regular environmental monitoring help verify that each area remains within its defined classification throughout both "at rest" and "in operation" states.

BMS & EMS CONTROL ON CPPs

In pharmaceutical HVAC systems, Building Management Systems (BMS) and Environmental Monitoring Systems (EMS) play crucial roles in maintaining and controlling critical parameters to ensure compliance with Good Manufacturing Practices (GMP) and product quality. Here's a brief explanation:

1. **Building Management System (BMS)**

   - **Control Functionality:**
   BMS is responsible for actively controlling HVAC parameters such as temperature, humidity, airflow, and pressure differentials. It ensures that the environment meets the required conditions for various pharmaceutical processes.
   - **Automation:**
   BMS automates the operation of HVAC equipment like air handling units (AHUs), chillers, and dehumidifiers. It adjusts settings based on real-time data to maintain optimal conditions.
   - **Energy Efficiency:**
   By optimizing HVAC operations, BMS reduces energy consumption while maintaining compliance with regulatory standards.

BMS & EMS CONTROL ON CPPs

2. Environmental Monitoring System (EMS)

- **Monitoring Functionality:**

EMS continuously monitors critical environmental parameters such as particle counts, microbial levels, temperature, and humidity. It ensures that these parameters remain within predefined limits

- **Data Logging:**

EMS records data for compliance and audit purposes. It provides evidence that environmental conditions were maintained during production.

- **Alarms and Alerts:**

If any parameter deviates from the acceptable range, EMS triggers alarms to allow immediate corrective action.

Integration of BMS and EMS

Together, BMS and EMS create a robust system where BMS controls the environment, and EMS verifies that the controlled conditions are maintained. This integration ensures both operational efficiency and regulatory compliance

GUIDELINES

- **EU GMP Guidelines:**

The European Medicines Agency (EMA) outlines HVAC requirements in its Annex 1 for sterile medicinal products, focusing on cleanroom classifications, air filtration, and environmental monitoring

- **ISO Standards:**

ISO 14644 series provide standards for cleanroom classifications and airborne particulate control, which are critical for pharmaceutical HVAC systems.

- **ASHRAE Standards:**

The American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) offers standards like ASHRAE 170 for ventilation in healthcare facilities, which can be adapted for pharmaceutical applications.

- **Local Regulatory Guidelines:**

Many countries have their own GMP guidelines that include HVAC requirements. For example, India follows Schedule M of the Drugs and Cosmetics Act.

- **The ISPE Good Practice Guide:**

Do provide detailed insights into designing and maintaining HVAC systems in line with Good Manufacturing Practices (GMP) and Good Engineering Practices (GEP). It covers critical aspects like contamination control, energy efficiency, and system validation, making it a valuable resource for pharmaceutical facilities.

CONCLUSION

HVAC systems must be designed, commissioned, qualified, and validated to meet the specific needs of pharmaceutical processes area classification. Along with process area classification following also must be maintained as per the standards and guidelines.

1. Temperature
2. Humidity
3. Differential Pressure
4. Air Changes Per Hour (ACPH)
5. Airflow Pattern
6. Particle Count
7. Microbial Count
8. HEPA Integrity
9. Recovery test

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