

UNIT-IV

Classification of clean area



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Aseptic Area

- Aseptic procedures are used to safeguard ophthalmic and parenteral goods by preventing microbiological and particle contamination.
- To eliminate pyrogen and harmful bacterial products, microbial contamination must be avoided.
- The preparation of terminally sterilized products (those sealed in a container and then sterilized) takes place in clean areas, whereas the preparation of non-terminally sterilized products takes place under aseptic conditions using sterile materials, or by sterilization through filtration before being placed in sterile packaging.

Clean Area Classification

- The clean or buffer room is the secondary engineering control.
- It houses the primary engineering controls (LAFH: laminar air flow hood) where the aseptic compounding is actually performed.
- Clean room is a specially constructed enclosed area, which contains one or more clean zones, where the concentration of airborne particles is controlled using HEPA filters, continuous air circulation, and a physical barrier to non-filtered (or outside) air.
- Clean rooms establish appropriate environmental levels for airborne particulates, temperature, humidity, air pressure, and airflow patterns.
- Clean rooms are categorized by their constant air quality or class.

Table 4.1: Classes of Clean Rooms and their Properties

Clean Room	Properties
Class 10,000 (ISO class 7)	10,000 or less particles of 0.5 μ and larger size exist in a given cubic foot of air.
Class 1,000 (ISO class 6)	1,000 or less particles of 0.5 μ and larger size exist in a given cubic foot of air.
Class 100 (ISO class 5)	100 or less particles of 0.5 μ and larger size exist in a given cubic foot of air.

Lower the classification number, cleaner is the air.

Apart from the above mentioned basic components, a clean room also includes:

- 1) UV irradiation,
- 2) Air-lock entry portals,
- 3) Special filtration or treatment systems for incoming air,
- 4) Sticky mats for removing particulate matter from shoes, and
- 5) Positive room air pressure for controlling entry of contaminants from adjacent rooms.

Clean rooms are divided into different classes in standards. Table 4.2 lists the equivalence of classes from different international standards. For manufacturing sterile products, a certain classification (table 4.3) with grades A to D are characterised to activity category (tables 4.3 and 4.4) is used.

Table 4.2: Class Limits for Federal 209D and ISO Standards

Class	Measured Particle Size (Micro meter)						
	ISO	0.1	0.2	0.3	0.5(a)	1.0	5.01
Federal 209 D							
1	3	1000	237	102	(1)	8	
10	4	10000	2370	1020	(10)	83	
100	5	100000	23370	10200	(100)	832	29
1000	6	1000000	237000	102000	(1000)	8320	293
10000	7				(10000)	832000	2930
100000	8				(10000)	8320000	293000

(a) - Particle count for this particular size is per ft while others are per m.

Table 4.3: Air Particle Classification System for the Manufacturing of Sterile Products

GRADE	Maximum Permitted Number of Particles per m Equal to or Above			
	At Rest (b)		In Operation (b)	
	0.5µm (d)	5µm	0.5µm (d)	5µm
A	3500	0	3500	0
B(a)	3500	0	350000	2000
C(b)	350000	2000	3500000	20000
D(c)	3500000	20000	Not defined (c)	Not defined (d)

Remarks

- 1) In order to reach the air grades B, C, and D, the number of air changes should be related to the room size, and the equipment and personnel in the room. The air system should be provided with HEPA filters for grades A, B, and C.
- 2) After 15-20 minutes of "clean up" period, an unmanned state (no manual activity) should be received.
- 3) Appropriate alert and action limits should be fixed for particulate and microbiological monitoring results. A corrective action in the operating procedures should be taken in case these limits are exceeded. The need for other parameters (like temperature, relative humidity, etc.) depends on the nature of product and manufacturing procedure. These parameters do not have any relation with the purifying classes.

Table 4.4: Terminally Sterilised Products

Grade	Examples of Operation
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of product.
D	Preparation of solutions and components for subsequent filling.

Most products should be prepared in grade D environment; while grade C environment should be used in case of an unusual risk.

Table 4.5: Aseptic Parameters

Grade	Examples of Operation
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered.
D	Handling of components after washing.

- The components after washing should be handled in grade D environment.
- The sterile starting material should be handled in grade A environment with grade B background.
- Solutions to be sterile filtered should be prepared in grade C environment; while if not filtered, the preparation should be done in grade A environment with grade B background.

- The aseptically prepared products should be handled and filled in grade A environment with grade B background.
- The sterile ointments, creams, suspensions, and emulsions should be prepared and filled in grade A environment with grade B background, when the product is exposed and is not subsequently filtered.
- Control of purity of zones by the particles in operation state and microbial control at an aseptic production area is required; and the recommended levels are listed in table

Table 4.6: Recommended Limits for Microbial Contamination in the Operation State (Average Values)

GRADE	Air Sample, cfu/m ³	Settle Plates (Diameter 90mm), cfu/4 hours (a)	Contact Plates (Diameter 55mm), 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	-

(a) - Individual settle plates are exposed for 4 hours or less; cfu - colony-forming unit.

Warning limitation and action for contamination by particles and microbes depend on the controlling results. Also corrective action should be provided in case of exceeding the above limits.