guidelines and follow all regulatory and safety procedures. Some specific responsibilities of this department could include review of standard operating procedures (sops) and batch/production records; investigation into any procedural or operational error and deviations from sops and/or batch/production records; system inspections/audits; regular cGMP training to personnel; and validation of facilities, equipment, and testing procedures. Validation is the demonstration that a piece of equipment, process, or test performs according to specification so that the data or the products generated are credible.

Applications

Facilities

Facility design should provide for unidirectional flow of materials, product, and personnel. Production suites should be on separate heat, vacuum, and air conditioning (HVAC) systems that provide classified, preferably HEPA (high-efficiency particulate air filter)-filtered air. Airflows need to be balanced within the production areas to maintain the classification.

There should be designated ''clean'' corridors for entry into production areas. Personnel are required to gown in pressurized entry air locks before accessing the production suites. Exit from production areas should also be through dedicated air locks, where degowning can occur prior to exiting to the return corridor. If possible, separate personnel and material air locks should provide access to the production areas. All systems must be qualified or validated to ensure that they function to specifications, and sops must be present to define the use of all facilities. Containment of microorganisms must also be achieved to avoid their release into the environment. Biological wastes require special equipment for decontamination prior to release.

The word ''facility'' includes, besides manufacturing and testing, the areas for generating various utilities such as water, gases, and steam. It is essential to understand the requirements of facility design in the light of the type of product to be manufactured, the quality of product to be handled, and the type of equipment and the conditions required to achieve desired output.

Environmental Conditions for Production of Vaccines. The manufacture of sterile pharmaceutical products including vaccines needs specified environmental categories to minimize the risk of contamination by microorganisms or particulate matter. There are four general category classifications.

Grade a: The local zone of high-risk operations (which involves filling, stoppering, exposure of open ampoules or vials, or making aseptic connections). Usually provided using a laminar airflow work station with a homogeneous air velocity of 0.45 m/sec + 20% at the working position.

Grade b: This is usually a background environment for grade a.

Grades c and d: For operations that are of less critical stages in the manufacture, but still require higher environmental conditions than those existing normally in the laboratory.

The airborne particulate classification for these grades is given in Table 2.

Not only are pharmaceutical products vulnerable to the presence of particulate matter they are also vulnerable to bacterial contamination. Air forced through HEPA filters keeps the bacterial contamination generated by the operators away from the product in a class a area. The background environmental condition, that is, class b for class a, would remove the generated particles and bacteria from the clean environment back to the air-handling unit via the return air duct. Manufacturers should monitor microbiological units during operations (Table 3).

To achieve the prescribed environmental and cleanliness standards, the prescribed manufacturing process needs to be classified into activities on the basis of the cleanliness of operations (Table 4).

Table 2 Airborne Particulate Classifications

	At rest[a]		In operation	
Grade	Maximum permitted number of particles/m^3 equal to or above			
	0.5 μm	5.0 μm	0.5 μm	5.0 μm
a	3500	0	3500	0
b[b]	3500	0	350,000	2000
c[b]	350,000	2000	3,500,000	20,000
d[b]	3,500,000	20,000	Not defined[c]	Not defined[c]

[a]The guidance given for the maximum permitted number of particles in the ''at rest'' condition corresponds approximately to the U.S. Federal standard 206 e and the ISO classifications as follows: grades a and b correspond with class 100, m 3.5, ISO 5; grade c with class 10,000, m 5.5, ISO 7, and grade d with class 100,000, m 6.5, ISO 8.

[b]To reach the b, c, and d air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades a, b, and c.

[c]The requirement and limit for this area will depend on the nature of the operations carried out.

Table 3 Recommended Limits of Microbial Contamination

Grade	Air sample cfu/m^3	Settle plates (diameter 90 mm), cfu/4 hr[a]	Contact plates (diameter 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	–

These are average values.

[a]Individual settle plates may be exposed for less than four hours.

Abbreviation: cfu, colony-forming units.

Table 4 Examples of Activities in Classified Areas

Grade	Examples of operations for terminally sterilized products
a	Filling of products, when unusually at risk
c	Preparation of solutions, when unusually at risk. Filling of products
d	Preparation of solutions and components for subsequent filling.
Grade	**Examples of operations for aseptic preparations**
a	Aseptic preparation and filling
c	Preparation of solutions to be filtered
d	Handling of components after washing