3.5 Pharmaceutical Cleanroom Classification

Cleanrooms used for pharmaceutical manufacturing have their own standards. The two most widely used are those published by the European Union and the USA.

3.5.1 European Union Guide to Good Manufacturing Practice

The most recent pharmaceutical standard used in Europe came into operation on January 1997. This is called 'The rules governing medicinal products in the European Union. Volume 4. Good manufacturing practices - Medicinal products for human and veterinary use'. It is often called the European Union Guide to Good Manufacturing Products (EU GGMP). This is available in various languages of the EU. Information as to where the standard can be obtained is given in Chapter 4.

For the manufacture of sterile medicinal products four grades of airborne cleanliness are given. The airborne particulate classification for these grades is given in Table 3.4.

Table 3.4 Airborne classification in the EU GGMP

	Maximum permitted number of particles/m^3 equal to or above			
Grade	**at rest (b)**		**in operation**	
	0.5 μm	5 μm	0.5 μm	5 μm
A	3 500	0	3 500	0
B(a)	3 500	0	350 000	2 000
C(a)	350 000	2 000	3 500 000	20 000
D(a)	3 500 000	20 000	not defined (c)	not defined (c)

Notes
(a) In order 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.
(b) The guidance given for the maximum permitted number of particles in the 'at rest' condition corresponds approximately to the US Federal Standard 209 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.
(c) The requirement and limit for this area will depend on the nature of the operations carried out.

The particulate conditions given Table 3.4 for the 'at rest' state should be achieved after a short 'clean up' period of 15–20 minutes (guidance value), after the completion of operations.

Examples of operations to be carried out in the various grades are given in the Table 3.5. The particulate conditions for a grade A zone that is in operation should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

Table 3.5 Examples of cleanroom conditions required for different operations

Grade	Examples of Operations for Terminally Sterilised 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.

Microbiological monitoring is also required to demonstrate the microbiological cleanliness of the cleanroom during production. The recommended limits are given in Table 3.6.

Table 3.6 Recommended limits for microbial contamination

Grade	Air Sample cfu/m^3	Settle Plates (diam. 90 mm), cfu/4 hours (b)	Contact Plates (diam. 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	-

Notes

(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.
(c) Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.

The air classification required for a cleanroom that has an isolator used to protect against contamination depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.

Blow/fill/seal equipment used for aseptic production, which is fitted with an effective grade A air shower, may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non-viable limits 'at rest', and the viable limit only when in 'operation'. Blow/fill/seal equipment used for the production of products for terminal sterilisation should be installed in at least a grade D environment.

3.5.2 Guideline on Sterile Drug Products Produced by Aseptic Processing.

This document is produced by the Food and Drug Administration (FDA) in the USA and published in 1987. Information on how to obtain this document can be found in the Chapter 4.

The FDA defines two areas in aseptic processing that are of particular importance to drug product quality. These are the 'critical area' and the 'controlled area'. A 'critical area' is described in the FDA document as:

> *'one in which the sterilized dosage form, containers, and closures are exposed to the environment. Activities that are conducted in this area include manipulations of these sterilized materials/product prior to and during filling/closing operations'.*

The 'controlled area' is described as:

> *'an area in which it is important to control the environment, is the area where unsterilized product, in-process materials, and container/closures are prepared. This includes areas where components are compounded, and where components, in-process materials, drug products and drug product contact surfaces of equipment, containers, and closures, after final rinse of such surfaces, are exposed to the plant environment'.*

The environmental requirements for these two areas given in the Guide are as follows:

3.5.2.1 Critical areas

The FDA guidelines give the following information:

> *'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 (Class 100) when measured not more than one foot away 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 characterises 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 is acceptable'.

3.5.2.2 Controlled areas

The FDA Guidelines give the following information:

'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 (Class 100,000) 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'.

Acknowledgements

Table 3.3 and Figure 3.2, as well as extracts of ISO 14644-1 are reproduced by permission of the British Standards Institution.