LIGHTHOUSE
WORLDWIDE SOLUTIONS

CLEANROOM GRADES
ABCD EXPLAINED

Lighthouse Worldwide Solutions

Overview

Clean rooms are precision-controlled environments crucial in manufacturing and scientific research. Operations within these areas are meticulously separated, distinguishing between terminal sterilization and aseptic processes. Clean areas are categorized based on specific environmental requirements for each operation, ensuring meticulous contamination prevention - an essential aspect of product integrity and safety.

An Overview of Cleanroom Grades

A clean room is an environment, typically used in manufacturing or scientific research that has a low level of environmental pollutants such as dust, airborne microbes, aerosols particles and chemical vapors. More accurately, a clean room has a controlled level of contamination that is specified by the number of particles per cubic meter at a specified particle size.

EU: EudraLex vol. 4 Good Manufacturing, "Annex 1, Manufacture of Sterile Medicinal Products" "The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency".

The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.

Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.

In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state. The "at-rest" state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

The EU GMP Annex 1 outlines three phases that need to be performed:

1. Certification: Each cleanroom and clean air device should first be classified.
2. Monitoring: The cleanroom should then be monitored to verify that conditions are being maintained relative to product quality.
3. Data review: The data accrued from the monitoring must be reviewed in light of the risk to finished product quality.

Cleanroom Grades Specified

The "in operation" and "at rest" states should be defined for each clean room or suite of clean rooms. For the manufacture of sterile medicinal products 4 grades can be distinguished.

Grade A:
Grade A is the cleanest, for sterile operations in a cleanroom. The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

Grade B:
For aseptic preparation and filling, this is the background environment for the grade A zone.

Grade C and D:
Clean areas for carrying out less critical stages in the manufacture of sterile products.
Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1.
Classification should be clearly differentiated from operational process environmental monitoring.
The maximum permitted airborne particle concentration for each grade is given in the following table.

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		**In operation**	
Grade	**0.5 µm**	**5.0µm**	**0.5 µm**	**5.0µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Activities By Grade

Grade A Activities:
Grade A activities include any sterile filling operations or any operations where the product could be at risk. Product exposure to contamination is the highest risk in Grade A environments where vials and ampoules are opened and exposed prior to filling operations and a higher level of environmental monitoring is required in these critical zones.

Grade B Activities:
A Grade B environment typically supports the grade A sterile zone it provides the background environment for grade A zone items needing aseptic preparation and filling.

Grade C/D Activities:
Areas graded C and D are used for performing less critical tasks that are carried out during less critical stages in the manufacturing process.