1 Purpose

The purpose of this Guideline is to describe the requirements for meeting current Good Manufacturing Practice (cGMP) compliance requirements for new and upgraded facilities to be used for the manufacturing of any sterile and non sterile product. The Guideline also aims to provide recommendations on how to achieve compliance with the requirements.

This Guideline defines a consistent approach for establishing facilities for the manufacture of sterile and non-sterile products using the classification set out in, EU Good Manufacturing Practice (GMP) Annex 1, FDA 21 Code of Federal Regulation (CFR) and International Standardization Organization (ISO) 14644-1.

Specific technical details are beyond the scope of this document; however, individuals are referred to the International Society For Pharmaceutical Engineering (ISPE) Pharmaceutical Engineering Guides for New and Renovated Facilities for essential detail.

Local legislation, regulatory requirements and engineering standards with respect to facilities will take precedence over this Guideline.

2 Scope and Applicability

This Guideline is applicable to all Operations, Marketing Companies (MCs) and Research and Development (R&D) sites, functions and departments undertaking work, or providing support services, required to meet cGMP or, in absence of a GMP standard, ISO standards. Manufacturing of Active Pharmaceutical Ingredient (API) is excluded from this Guideline.

3 Definitions

3.1 General Manufacturing Areas

Processing and packaging areas where GMP activities are taking place for non-sterile dosage forms. Minimum requirements are discussed with the recognition that additional engineering controls are needed as product potency, degree of separation, degree of exposure, extent of validation, and other considerations enter into particular site product mix and circumstances for example there are requirements for inhalation products being manufactured in Grade D.

3.2 Air Classification

Level (or the process of specifying or determining the level) of airborne particulate cleanliness applicable to a clean room and clean area, expressed in terms of EU Grades, which represents maximum allowable (in particles per cubic metre of air) for considered sizes of particles.

The comparison between EU Grades, FDA classification and ISO classes are defined in appendix A.

5.1.3 Access

For product safety and security reasons, doors to production and storage areas must be secured such that access is only given to authorized personnel. Emergency exits should be sealed for day-to-day operations but providing immediate exit in case of emergency.

5.2 Environmental Conditions

All environmental conditions for clean areas must be classified and maintained in accordance with requirements in EU GMP Annex 1 and FDA 21 CFR, Guidance for Industry "Sterile Drug Products By Aseptic Processing", September 2004, ISO 14644-1and IPSE Pharmaceutical Engineering Guides for New and Renovated Facilities, Volume 2, Oral Dosage Forms and Volume 3 Sterile Manufacturing Facilities as appropriate. Comparison tables for particles and microbiological organisms see Appendix A - B.

Sites manufacturing for global markets should adhere to the strictest requirements described in Appendix A – B in order to meet all market requirements.

5.2.1 Environmental Conditions for Sterile Manufacturing

Sterile manufacturing must take place in clean areas. The areas should be classified in accordance with the requirements in Appendix A - B.

All areas must be built and validated to meet these requirements.

The particulate conditions for Grade A 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, for example due to the generation of particles and droplets from the product itself. There should be written justifications for any situation or process steps where this could apply.

The particulate conditions for the at rest state should normally be achieved in the unmanned state after a short clean up period of 15 - 20 minutes after completion of operations. This cleanup period should be validated and periodically monitored.

In some cases, the processing room and the adjacent clean rooms have the same classification. Maintaining a pressure differential between the processing rooms and the adjacent rooms can provide beneficial separation.

In order to reach Grade A, B and C the number of air changes should be related to the activity of the room.

Re-circulation of air within clean areas should not be practiced where the activities are creating dust. Re-circulation should preferably not be used to re-circulate air from areas where different products are handled. In cases where re-circulation is practiced the air should pass a filter system of an appropriate filter

also minimized and protection is provided against contamination during filling and closing of units.

Grade	Examples of operations for blow/fill/seal technology
A	Blow/fill/seal equipment used for aseptic production.
C	The background environment for blow/fill/seal equipment used for aseptic production provided that Clean Area A/B clothing is used.
D	Blow/fill/seal equipment used for terminally sterilized production.

5.2.2 Environmental Conditions for Non-sterile Manufacturing

Non-sterile manufacturing should take place in general manufacturing areas. There are no cGMP requirements to classify these areas with the exemption of manufacturing of inhalation products, which must take place in Grade D. Good engineering practice (GEP) should dictate the basic requirements for these areas. The ISPE Pharmaceutical Engineering Guide for New and Renovated Facilities, Volume 2, Oral Solid Dosage Forms should be consulted.

Re-circulation of air within general manufacturing areas should be justified and it should be taken into account process activities that create dust. In cases where re-circulation is practiced the air should pass a filter system of an appropriate filter efficiency to avoid cross-contamination and to prevent recirculation of dust from production. In areas where air contamination occurs during production, consideration should be given to provide localized exhaust systems or other means to minimize potential for cross contamination.

5.3 Production Areas

5.3.1 Layout

The layout of areas must minimize the possibility of product mix-ups. The adequacy of the working and in-process storage space must permit the orderly and logical positioning and separation of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

5.3.2 Air Treatment (HVAC)

5.3.2.1 General

Production areas should be effectively ventilated, by air handling units (including filtration control and when necessary temperature and humidity control) appropriate to the products handled, to the operating personnel, to the operations undertaken within them and to external environment.

Temperature and humidity controls should be considered in terms of potential adverse effect on the medicinal products during their manufacture and storage, or the accurate functioning of equipment. Areas were aseptic processing takes

Windows must be installed with tight connections to the wall. The number and area of horizontal surfaces in the installation must be kept to a minimum. Windows must be easy to clean, fixed and not capable of being opened.
Windows should be in level with walls and ceilings.

5.3.7 Sinks and Drains

Separate process and sanitary drainage must be provided. Drains must be of adequate size and, were connected directly to a sewer, must be provided with an air break or other mechanical device to prevent back-siphonage. They must be easy to clean. The floor must slope locally towards the drain. Overflow outlets should normally not be used.

Floor drains with minimal usage should be filled with vegetable oil or contain a trap primer in order to prevent the trap from drying out.

5.3.7.1 Special Requirements in Sterile Manufacturing

Sinks and drains should be prohibited in Grade A and B areas used for aseptic manufacture.

5.3.8 Installations

All permanent pipe work, light fittings, ventilation ducts and other services in classified areas should be designed and installed to avoid uncleanable recesses.

Services should run outside the processing areas and should be sealed into walls and partitions through which they pass. The sealed pass through should be designed to withstand vibrations.

Fixed equipment should be installed without any recesses where dirt can accumulate.

5.3.9 Airlocks

The use of airlocks should be considered as part of any manufacturing facility design. Airlocks are one means to control containment necessary due to process or product requirements.

Personnel airlocks may be necessary for connection of areas where dust-generating processes are performed or certain active substances are handled. Such airlocks should be provided with cleaning facilities as needed.

The airlocks must have a system in place to prevent the opening of entry and exit doors at the same time. This could be achieved by means of an interlocking system and the doors should be self-closing.

5.3.9.1 Special Requirements for Sterile Manufacturing

Personnel Airlocks

and/or dispensing. Operator comfort should be taken into account when setting the temperature and humidity requirements; particularly when operators are wearing suits made of synthetic non-breathing materials.

Appendix B - Comparison table microorganisms EU GMP Annex 1 and FDA Guidance for Industry "Sterile Drug Products Produced by Aseptic Processing".

EU GMP Annex 1					FDA		
Grade	Recommended limits for microbial contamination in operation (a)				Description (In Operation)	In operation	
	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		Microbiological Active Air Action Levels Cfu/m^3	Settle plates (diam. 90 mm) cfu/4 hours
A	<1	<1	<1	<1	Critical area (100)	<1	<1
B	10	5	5	5	Supporting Clean Area (10000)	10	5
C	100	50	25	-	Supporting Clean Area (100000)	100	50
D	200	100	50	-	Supporting Clean Area (undefined)	-	-

(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.
* - = not defined

