28th ad hoc meeting of GMP Inspection Services, 3rd / 4th July 2002
Item 7.1: (updated version, afternoon session July 4th, 2002)

Proposal for Revision of Annex 1 to the EU-GMP Guide

(prepared by a drafting group: Florence Benoit-Guyod, France; Paul Hargreaves, United Kingdom; Gerd Werner, Germany)

(***Drafting Note*:** changes to the text of the actual version of Annex 1 are shown in bold italic, deleted items are not shown)

Proposed text for Annex 1 (new)

Principle

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

Note:
***This** guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. Reference **should be** made to other compendia such as the EN/ISO Standards.*

General

1. 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.
2. 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.
3. 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 "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 : 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*** at the working position ***in open clean room applications.***
An uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.
The maintenance of laminarity should be demonstrated and validated.

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

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for these grades is given in the following table.

	at rest ***(b)***		in operation ***(b)***	
Grade	maximum permitted number of particles/m^3 equal to or above ***(a)***			
	0,5 µm ***(d)***	5 µm	0,5 µm ***(d)***	5 µm
A	3 500	***1 (e)***	3 500	***1 (e)***
B ***(c)***	3 500	***1 (e)***	350 000	2 000
C ***(c)***	350 000	2 000	3 500 000	20 000
D ***(c)***	3 500 000	20 000	not defined ***(f)***	not defined ***(f)***

Notes:

(a) ***Particle measurement based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal to or greater than the threshold stated.***
When monitoring the concentration of particles in clean room areas class A or B a continuous measurement of particles should be guaranteed in principle.
For routine testing the total sample volume at each point should not be less than 1 m^3 at least for Grades A and B, preferable also in Grade C.

(b) ***The particulate conditions given in the table for the « at rest » state should be achieved in the unmanned state after a short « clean up » period of 15-20 minutes (guidance value) after completion of operations. The particulate conditions for grade A "in operation" given in the table 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***.

(c) *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*

*provided with appropriate **terminal** filters such as HEPA for grades A, B and C.*

(d) *The guidance given for the maximum permitted number of particles in the "at rest" **and "in operation"** condition corresponds approximately to the **cleanliness classes in** the **EN**/ISO **14644-1 at a particle size of 0.5 µm.***

(e) ***It is expected to get these areas completely free from particles sized equal or greater than 5 µm. As it is impossible to demonstrate absence of particles with any statistical significance the limits are set to 1 particle / m^3. During the clean room qualification it should be shown that the areas could be maintained within the defined limits.***

(f) *The requirement and limit for this area will depend on the nature of the operations carried out.*

Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. The parameter settings should be such not to interfere with the defined cleanliness standard. For temperature and relative humidity, the general accepted guidance values are 18 +/- 2 °C and 40% to 60 %, respectively

Personnel

20. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session~~***, or at least once a day if monitoring results justify it***~~. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.