European Medicines Agency
Inspections

London, 21 September 2005
Doc. Ref: EMEA/INS/GMP/318222/2005/**Correction**

GMP Annex 1: Proposals for amendment to the environmental classification table for particles and associated text, amendment to section 42 concerning acceptance criteria for media simulations, amendment to section 52 concerning bio-burden monitoring, and additional guidance in section 88 on the sealing of vials.

The existing text of clause 3 remains unchanged up to and including the following:

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

The remaining text of clause 3 up to but not including the following:

Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

and clause 4 is replaced by:

Clean room and clean air device classification

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.

	at rest		in operation	
Grade	Maximum permitted number of particles/m^3 equal to or above			
	0.5 μm	5.0μm	0.5 μm	5.0μm
A	3 500	1*	3 500	1*
B	3 500	1*	350 000	2 000
C	350 000	2 000	3 5000 000	20 000
D	3 500 000	20 000	Not defined	Not defined

* The maximum permitted number of particles at ≥5.0μm is established at 1/ m^3 but for reasons related to false counts associated with electronic noise, stray light, etc. a limit of 20/m^3 could be considered.

For classification purposes, in Grade A zones, a minimum sample volume of 1m^3 should be taken. Grade A and Grade B (at rest) is similar to EN ISO Class 5 for particles ≥0.5 μm. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size. It should be noted that this will give rise to a sampling time of about 35 minutes at each location when using a particle counter with a sample rate of 28.3 litre/minute (one cubic-feet per minute).

Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0μm particles in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.

"In operation" classification may be demonstrated during media fills because of the worst-case simulation required for this.
EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

5. Clean room and clean air device monitoring
Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on formal risk analysis study and results obtained during the initial classification of rooms and/or devices.

For Grade A zones a continuous or frequent sampling particle monitoring system should be used, except where justified, e.g. the filling of live virus vaccines. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. Such systems may consist of independent particle counters; or have one particle counter that is linked to a number of sampling ports sequentially via a tubing manifold system. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be validated. The Grade A zone should be monitored at such a frequency that all interventions and other transient events would be captured and alarms triggered if excursions from defined operating norms occur.

The sample sizes taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.

6. In Grade A and B zones, the monitoring of the 5.0 μm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of μm particle counts ≥5.μmay be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnosis of poor practices during machine set-up and routine operation.

7. The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period of 15-20 minutes (guidance value) in an unmanned state after completion of operations. It is accepted that it may not always be possible to demonstrate low levels of particles ≥5 μm at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

8. For Grade D areas in operation, the requirements and limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.

The new clause 9 takes up the existing text of clause 3 at the following point:

Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

The existing clauses from 5 to 41 are unchanged but re-numbered as 10-46. Clause 47 (formerly clause 42) is changed as follows:

47. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following recommendations apply:

i When filling fewer than 5000 units, no contaminated units should be detected.

ii When filling 5,000 to 10,000 units:
1 contaminated unit should result in an investigation, including consideration of a repeat media fill.
2 contaminated units are considered cause for revalidation, following investigation.

iii When filling more than 10,000 units:
1 contaminated unit should result in an investigation.
2 contaminated units are considered cause for revalidation, following investigation.

Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

Clauses 43 to 51 are unchanged but re-numbered as 48-56. Clause 57 (formerly clause 52) is changed as follows:

57. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

Clauses 53 to 87 are unchanged but re-numbered as 58-92. Clause 93 (formerly clause 88) is changed as follows:

93. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

    Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times, from the time of partial stoppering to capping.

    The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place. Vials should be maintained in Grade A environment until the cap has bee crimped. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction. The capping station may not be able to meet Grade A conditions for non-viable particles in the “in operation” condition but should meet the microbiological requirements.

Clauses 89 to 93 are unchanged but re-numbered as 94-98.