Annex 1 2022 Comparison Factsheet: Grade Level Detail

Previously the limits for microbial contamination stated an average of less than one cfu.
In the 2022 version of Annex 1, the limit is zero.

2008 Annex 1: Clean room and clean air device monitoring.

19. Recommended limits for microbiological monitoring of clean areas during operation:

	Recommended limits for microbial contamination (a)			
Grade	Air sample cfu/m3	Settle plates (diameter 90 mm) cfu/4 hours (b)	Contact plates (diameter 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	30	-

(a) These are average values.

(b) Individual settle plates may be exposed for less than 4 hours.

20. 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.

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2022 Annex 1: Section 9 Environmental and personnel monitoring – viable particle

	Table 6: Maximum action limits for viable particle contamination.			
Grade	Air sample cfu/m3	Settle plates (diam. 90 mm) CFU /4 hours(a)	Contact plates (diam. 55mm), CFU / plate(b)	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth(c)			
B	10	5	5	5
C	100	50	25	-
D	200	100	30	-

(a) - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).
- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.
- Individual settle plates may be exposed for less than 4 hours.

(b) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function.

(c) It should be noted that for grade A, any growth should result in an investigation.

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The 2022 revision of Annex 1 includes a greater level of detail describing requirements and guidance on operations in Grade A – D facilities.

Grade	Wording in 2022 Annex 1 4.4 For the manufacture of sterile products, there are four grades of cleanroom/zone.'
Grade A	The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.
Grade B	For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be cosidered where isolator technology is used (see paragraph 4.20).
Grade C + D	These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation/filling of terminally sterilised products. (See section 8 for the specific details on terminal sterilisation activities).