

Proposed Changes to EU GMP Annex 1 and Draft Revision ISO/DIS 14644-3: 2016

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Abstract

This paper concentrates on the effect on Cleanroom Classification and Monitoring due to the changes proposed in Sections 5 and 9 of the 50 page guideline EU GMP Annex 1 Revision Draft December 2017, such as the removal of particle sizes higher than 5 micron for the qualification of rooms but not for monitoring. The proposed changes in ISO/DIS 14644-3:2016 are discussed, including enhanced guidance on testing air volumes, room pressures and recovery time; and particle counting for classification has been aligned to ISO 14644-1:2015.

Keywords

Revisions to EU GMP Annex 1 and ISO 14644-3

Introduction

Improvements to equipment and the onslaught of new technology have necessitated changes to the Guideline and ISO standard mentioned in the title. This paper discusses the impact on the pharmaceutical industry and life sciences industries in particular, of the proposed changes. Although these revisions have been published more than nine years after the previous versions appeared, they are still a welcome step forward.

EU GMP Revision 2009 (Current Version, Being Updated)

Table 1: Maximum permitted airborne particle concentration for each grade: EU GMP Annex 1: 2009

Maximum permitted number of particles per m ³ ≥ the tabulated size				
Grade	At rest		In operation	
	≥ 0.5 μm	≥ 5.0 μm	≥ 0.5 μm	≥ 5.0 μm
A	3,520	20 (ISO 5 = 29)	3,520	20
B	3,520	29	352,000	2,900 (ISO 7 = 2,930)
C	352,000	2,900 (ISO 7 = 2,930)	3,520,000	29,000 (ISO 8 = 29,300)
D	3,520,000	29,000 (ISO 8 = 29,300)	Not defined	Not defined

This paper was presented by the author at ISCC 2018 in September at The Hague, Netherlands

History and Background of Annex 1 Revisions

The original version of EU GMP Annex 1 was revised in 1996, 2003, 2005, 2007 and 2009. However, there has not been a complete review of the Guideline since it was originally issued. Since then, there have been many changes in technologies and in GMP consequent to the adoption of ICH Q9 and Q10 guidelines.

In 2012, The German Authorities (ZLG) issued a concept statement to EMA Inspectors' Working Group proposing revision of the Annex, and a subsequent request was made to PIC/S for support in the updation.

In 2014, a PIC/S Working Group was set up. On December 20, 2017 the European Commission published the long awaited revision draft of Annex 1, 'Manufacture of Sterile Medicinal Products', of the EU Guideline for Good Manufacturing Practice for Drug Products and Drug Substances. The resultant draft has increased in length from 16 to 50 pages. Also, there are 269 different clauses now, whereas in the 2009 version there were 100 clauses.

A very important point to note is that for classification, only airborne particles equal to or greater than 0.5 μm are to be measured. Particle sizes higher than 5 μm have been removed from the qualification of rooms. This measurement should be performed both at rest and in operation. The maximum permitted airborne particle concentration for each grade is given in Table 2. For classification, airborne particles ≥0.5 μm should be measured. This measurement should be performed both at rest and in operation. ISO class equivalents are usefully included alongside

EU GMP grades. The exclusion of $\geq 5.0 \mu\text{m}$ applies to classification only; *monitoring of these particles still remains a requirement for monitoring of aseptic processing and other cleanroom activities* (see Table 5 of Annex). Requirements for Grade C and D cleanroom routine monitoring are also given in the draft Annex. In addition, there is a requirement to use risk management techniques to justify the locations, number and frequency of samples for routine monitoring of Grade C and D areas, in relation to both non viable particle count and viable count monitoring.

Non-viable Monitoring in EU GMP Annex 1 December 2017 Draft

Table 2: Maximum permitted airborne particle concentration during classification (Table 1 of Annex)

Maximum permitted number of particles $\geq 0.5 \mu\text{m}$			
Grade	At rest $\geq 0.5 \mu\text{m}$ per m^3	In operation $\geq 0.5 \mu\text{m}$ per m^3	ISO classification in operation/at rest
A	3,520	3,520	5/5
B	3,520	352,000	5/7
C	352,000	3,520,000	7/8
D	3,520,000	Not Defined	8

Airborne Particle Concentration for Monitoring of Non-viable Contamination

Table 3: Recommended limits for airborne particle concentration for the monitoring of non-viable contamination (Table 5 of Annex)

Grade	Recommended maximum limits for particles $\geq 0.5 \mu\text{m}$		Recommended maximum limits for particles $\geq 0.5 \mu\text{m}$	
	In Operation $\geq 0.5 \mu\text{m}/\text{m}^3$	At rest $\geq 0.5 \mu\text{m}/\text{m}^3$	In Operation $\geq 5 \mu\text{m}/\text{m}^3$	At Rest $\geq 5 \mu\text{m}/\text{m}^3$
A	3,520	3,520	20	20
B	35,200	3,520	2,900	29
C	352,000	352,000	29,000	2,900
D	Set a limit based on the risk assessment	3,520,000	Set a limit based on the risk assessment	29,000

Frequency of Classification of Cleanrooms

ISO 14644-2:2015 says, "Periodic classification testing shall be undertaken *annually*."

Frequency of re-testing the cleanroom is no longer dictated by its Class; it has to be done annually. Previously it was 6 months for ISO Class 5. *However*, EU GMP Annex 1 December 2017 Draft Revision states in Clause 5.29: "Cleanrooms should be requalified periodically and after changes to equipment, facility or processes based on the principles of Quality Risk Management. For grade A and B zones, the maximum time interval for requalification is *6 months*. For grades C and D, the maximum time interval for requalification is 12 months."

Minimum Sample Volume to EU GMP Annex 1

Old EU GMP Annex 1:2009 states: "For classification purposes in Grade A zones, a minimum sample volume of 1m^3 should be taken per sample location". *However*, the new December 2017 Draft Revision to EU GMP Annex 1 does not mention 1m^3 , and states (Clause 5.26): "For initial classification, the minimum

number of sampling locations can be found in ISO 4644 Part 1." It also states that a higher number of samples and sample volume are typically required for aseptic processing room and the immediately adjacent environment (grade A/B), to include consideration of all critical processing locations such as point of fill stopper bowls.

Sample Tubing Length

Clause 6.9 states that particle counters should be qualified *including sampling tubing*. Portable particle counters with a short length of sample tubing should be used for qualification purposes. How do we 'qualify' the sample tubing, and what exactly is meant by 'short length' – 1 metre, or 3 metres, or 5 metres? The new ISO 1644-1:2015 Annex C (*Informative, not Mandatory*) – *Counting and sizing of airborne macroparticles* states in Clause C.4.1.2: "For sampling of particles larger than and equal to $1 \mu\text{m}$, the transit tube length should not exceed the manufacturer's recommended length and diameter, and will typically be no longer than *1 metre in length*."

What about the radius of the bend in sample tubing? No guidance is given for this.

ASTM F50 is helpful in this regard. If a flexible transit tube is to be used, no radius of curvature below 15 cm shall be used.

Continuous Non-viable Monitoring

No real change from the previous version except that the flow rate of the particle counter, viz. 1 cfm, is specified now.

Clause 9.14 says that for grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

Clause 9.15 reiterates that grade A zones should be monitored continuously and with a suitable sample size (at least 28 litres, i.e. one cubic foot per minute), so that all interventions, transient events and any system deterioration would be captured and alarms triggered if permissible limits are exceeded.

Clause 9.16, as before, states that EU recommends that a similar system be used for grade B zones, although the sample frequency may be decreased.

Continuous Viable Monitoring

A new section has been introduced requiring *continuous viable monitoring in Grades A & B*. Clause 9.27 specifies that continuous monitoring in grade A and B areas should be undertaken for the full duration of critical processing, including equipment assembly and filling operations. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations would be avoided.

Draft International Standard ISO/DIS 14644-3

Time Frame for new ISO 14644-3

The latest cleanroom test methods are highlighted in the recently issued ISO Draft International Standard (DIS) 14644, *Cleanrooms and associated controlled environments — Part 3: Test methods*.

The submission date was October 27, 2016. Voting began on December 16, 2016 and terminated on March 9, 2017. FDIS have not been issued yet, and the final Standard will be published probably in the last quarter of 2018 or early 2019. CCSI has submitted its comments/suggestions for corrections and amendments via ICCCS.

Proposed Changes

- Particle counting for classification has been aligned with ISO 14644-1:2015
- More guidance on testing air volumes
- More guidance on testing room pressures
- More guidance on recovery time test
- Revision of text on filter testing based on particle counting

Measurement methods for classification by particle concentration have been removed from ISO 14644-3 and placed in ISO 14644-1. This standard is intended for use by cleanroom certifiers as well as end users.

ISO/DIS 14644-3 specifies performance tests for two types of cleanrooms – unidirectional and non-unidirectional – in three occupancy states (as-built, at-rest, and operational).

Clause A3 Pre-test Conditions

Here, it is mentioned that special care should be taken while determining the sequence for performing tests for cleanroom performance, as the results of each cleanroom test may be dependent upon other pre-conditioning requirements being met.

Cleanroom Tests

One or more classification tests for cleanrooms have to be carried out in order to classify an installation. The tests applied will be determined by the cleanliness attributes of interest.

Attribute Tests for Cleanrooms and Clean Zones

Table 4: Attribute tests (Table 1 of ISO/DIS 14644-3)

Attribute tests for cleanrooms and clean zones	Referenced in
Classification tests for cleanrooms and clean zones (ACP)	ISO 14644-1 and ISO 14644-2
Classification of surface cleanliness by particle concentration (SCP)	ISO 14644-9
Classification of air cleanliness by chemical concentration (ACC)	ISO 14644-8
Classification of surface cleanliness by chemical concentration (SCC)	ISO 14644-10

Supporting Tests

Table 5: Supporting tests (Table 2 of DIS 14644-3)

Supporting tests	Reference in ISO 14644-3: 20XX		
	Principle	Procedure	Apparatus
Air pressure difference test (required)	4.2.1	B.1	C.1
Airflow test (required)	4.2.2	B.2	C.2
Airflow direction test and visualization	4.2.3	B.3	C.3
Recovery test	4.2.4	B.4	C.4
Temperature test	4.2.5	B.5	C.5
Humidity test	4.2.6	B.6	C.6
Installed filter system leakage test	4.2.7	B.7	C.7
Containment leak test	4.2.8	B.8	C.8
Electrostatic and ion generator tests	4.2.9	B.9	C.9
Particle deposition test	4.2.10	B.10	C.10
Segregation test (new test)	4.2.11	B.11	C.11

Guidance on Typical Time Intervals for Periodic Testing (New)

The following testing moments have been identified:

- On installation: during the commissioning process
- At requalification:
 - After identified and rectified failure
 - After modification: when the installation, the cleanroom and/or its usage or the operational set points have been changed.
- Periodic retest (shown in Table A.2 of Annex)

To establish the appropriate interval for periodic testing, it is recommended to undertake a risk analysis.

The guidance below is provided to suggest typical maximum time intervals for periodic testing of important cleanroom performance parameters.

Table 6: Typical test frequency (Table A.2 of DIS 14644-3)

Type of selected test	Typical period to retest
Pressure differentials	12 months
Air supply volume in non-unidirectional airflow	12 months
Air velocity in unidirectional airflow	12 months
Installed filter system leakage – non-unidirectional airflow cleanroom	24 months
Installed filter system leakage – unidirectional airflow cleanroom	12 months
Air direction and visualization	..
Recovery rate	..
Containment leak	..
Particle deposition rates	..
Segregation tests	..
Temperature and Humidity	12 months
Electrostatic and ion generator	..

Summary of Proposed Changes to ISO 14644-3

- Clause 4.1.1 and Table 1: Description changed from ‘Required Test’ to ‘Attribute tests for cleanrooms and clean zones’.
- Clause 4.1.2 and Table 2: Description changed from ‘Optional Tests’ to ‘Supporting Tests’.
- Clause 4.2.11: New test added, called ‘Segregation Test’.
- Annex A: Name changed from ‘Choice of recommended tests of an installation and the sequence in which to carry them out’, to ‘Choice of supporting tests and checklist’.
- New Addition: A4 Guidance on typical time intervals for periodic testing.
- Airflow: Table A.1 Checklist.

- Previously, four Test Procedures were listed; now there are seven procedures.
- New section added: B7.3.9, 'Procedure for leakage scan test for installed ULPA filter system'.
- Apparatus specified in B.7.5.1 to B.7.5.4 should have a valid calibration certificate including suitable pneumatic or thermal aerosol generator to provide appropriate challenge aerosol concentration in the appropriate size range.
- B8.3 'Apparatus for containment leak test': the following apparatus should have a valid calibration certificate: B.8.3.1, Artificially generated aerosol source. Since these generators are mechanical in nature, they should not change throughout their life time. (Apparently the pressure gauges of the Laskin Nozzle (cold) and thermal (hot) aerosol generator must be calibrated annually.)
- C.7 'Installed filter system leakage test'. (Previously this was Clause C.6).
- Only linear aerosol photometer is now specified; logarithmic type has been removed.
- Only three parameters are now specified in Table C.6, viz. measuring limits, resolution, and maximum permissible error. (Earlier there were 10 items.)
- Under Clause B7.7, 'Test Reports', an additional item is to be recorded now, viz. specification of the filter.
- B.4 'Recovery Test' (previously B.12): this test is performed to determine the ability of the installation to reduce the concentration of airborne particles by dilution. (The previous clause said that the test is performed to determine the ability of the installation to eliminate airborne particles.) The recovery performance is evaluated by using the 100:1 or 10:1 recovery time and/or the cleanliness recovery rate. The 100:1 (or 10:1) recovery time is defined as the time required for decreasing the initial concentration by a factor of 100 times (or 10 times). Previously, only 100:1 test was mentioned; now 10:1 has been added.

Discrepancies Noticed and Clarifications Required

Segregation Test

The revision requires the addition of a segregation test method to assess the protective effect of a specific segregating airflow, e.g. across a doorway or across the perimeter of an area with a higher classification than the surrounding area. The test is performed by generating a sufficiently higher concentration in the lower classified area, i.e. the downstream side, measuring it as the reference concentration and counting the particle concentration just across the perimeter in the protected area, i.e. the upstream side.

Table 2 of the Annex, 'Supporting Tests', mentions 'Segregation Test 4.2.11 B.11 C.11'. However, this test is called 'Entrainment Test' in Table A.1: *Entrainment Test B.11, Light-scattering Discrete Particle Counter C.11.1*. This is confusing; it should either be called segregation test or entrainment test.

Also, the term Discrete Particle Counter has been replaced by Light Scattering Airborne Particle Counter in ISO 14644-1:2015, so this term should be followed.

Table A.2 —Typical Test Frequency

Several columns are blank, e.g. the period for recovery rate, and air containment. Perhaps ISO should refer to British Standards Institute National Annex NA (Informative) Table NA.1, 'Recommended schedule for testing cleanrooms', which gives details of these frequencies for various tests. However, the referred Annex states that the period should be 'continuous' for pressure differentials, whereas the ISO 14644/DIS-3 Table says it should be 12 months.

A.4 Guidance on Typical Time Intervals for Periodic Testing

This advises us to consider periodic classification testing according to ISO 14644-2 to establish the time intervals for periodic tests. However, the new ISO 14644-2:2015 covers only monitoring, and not classification.

Conclusion

When published in their final format and (hopefully) having addressed the discrepancies and followed the suggestions by various experts, these two documents will serve as valuable guidance for the cleanroom community. ❖