

Technical Review: European GMP Annex 1 – 2008 Edition

The GMP guidance for sterile manufacture was revised in 2003 to accommodate changes from various cleanroom standards and create a single unified cleanroom standard, ISO4644-1. The introduction to ISO 14644-1 states this as:

Annex 1 of the EC Guide to Good Manufacturing Practice (GMP) provides supplementary guidance on the application of the principles and guidelines of GMP to sterile medicinal products. The guidance includes recommendations on standards of environmental cleanliness for clean rooms. The guidance has been reviewed in the light of the international standard EN/ISO 14644-1 and amended in the interests of harmonisation but taking into account specific concerns unique to the production of sterile medicinal products.

The method to certify a cleanroom must comply with the rules and format of ISO14644-1 guidance. This new Annex includes a modified ISO standard which addresses sterile medicinal products. To support this, a table of cleanroom certification values that roughly translated to ISO 14644-1 was defined. For clarity, a series of notes appended the table. Unfortunately, the first, "Note a", caused certain confusion.

This confusion has been remedied in the 2008 release of the EU GMP Annex 1 which clearly outlines three phases that need to be performed:

1. **Certification:** Each cleanroom and clean air device should first be classified
2. **Monitoring:** the cleanroom should then be monitored to verify that conditions are being maintained relative to product quality
3. **Data Review:** Ensure that the data accrued from the monitoring be reviewed in the light of risk to finished product quality.

Certification

It is important to understand ISO14644-1 and how to certify a cleanroom in accordance with that standard. Rules on the number of sample points, sample point location, and volume of sample to be taken at each location need to be followed to conduct and document the certification, as well as the rules on statistical analysis of cleanroom data. Table 1 clarifies classification limits prescribed in ISO14644-1, based on the 2008 Revision.

Table 1. Cleanroom grade classifications

Maximum permitted number of particles per m ³ equal to or greater than the tabulated size				
At Rest			In Operation	
Grade	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Not defined	Not defined

Other certification expectations are also defined by the GMP. Sample volume for Grade A should be 1 m³ per sample location, and a minimum length of sample tubing should be used due to the high precipitation of 5.0 µm particles in transport tubing. Ideally, no sample tubing should be used. Also, re-certification of the cleanroom should follow the guidance given in ISO14644-2 – once per year for ISO Grade 6 and greater and once per 6-months for ISO Grade 5 and cleaner. Concessions are made for extending the ISO Grade 5 areas if a monitoring system has been implemented. Suitable times to perform certification are media fills or simulated filling runs.

Monitoring

After certification the room must be monitored, relative to risk, to prove that the aseptic manufacturing environment can and has been maintained. Particle Measuring Systems has published several [papers](#) regarding the types of systems suitable for monitoring based upon risk and how to implement such systems.

The Grade A zone, which is the environment of greatest potential risk to the finished product, should be monitored for the full cycle of production, including set-up. The frequency of monitoring should ensure that any interventions, short duration events, or general deterioration in conditions can be measured and alarms are triggered if alert/action limits are exceeded. This requirement essentially precludes the use of manifolds in these areas due to the sequential nature of the sampling being performed; concessions

are made for the use of manifolds if they have been sufficiently validated as suitable for the relevant manufacturing type.

Grade B areas follow the same rules as Grade A. However, the frequency of sampling can be reduced. Grade A is maintained under laminar flow, and so short burst events may be localized and of short duration, excluding some catastrophic failures. However, Grade B is turbulent mixed air flow and reflective of the general environment in which operators are present. A low level of continuous particulate activity in this area is normal and the system's response is to alarm when general control of this area is out of tolerance. Therefore, an immediate spike in contamination is less likely to have a significant impact on product quality. This becomes more pronounced when looking at background support areas beyond the zone in immediate proximity to the filling line or other Grade A areas.

In the 2003 GMP, there was confusion over the sample required for monitoring the Grade A and Grade B areas due to the phraseology used. The 1 m³ sample was to meet the calculation required by ISO 14644-1 and not a risk-based monitoring value. However, clarity is provided in the revised guidance:

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.

A system using a 28.3 l/min particle counter would ideally sample continuously, from set-up through the entire filling period and slightly beyond, taking minute-by-minute samples, normalizing data to counts/m³, and setting appropriate alarm and alert limits on the normalized values.

The key to monitoring is to be able to respond in a timely manner to events that show the area is no longer in environmental control.

Data Review

There is a relationship between non-viable particles in a cleanroom and the viable contaminants (USP <116>). Additionally, studies show the size of viable particulates free-floating in a cleanroom. When combining these two independent studies together, it is apparent that if you can control the large particles in a cleanroom, you can also demonstrate control over the viable risk in a cleanroom. Empirically this is difficult to show due to the statistics of the small numbers generated. That is, < 1 particle and < 1 CFU. As a result, the 5.0 µm particle size is of particular importance when reviewing environmental data within the cleanroom.



Figure 1. Lasair III particle counter

Occasional high counts may be due to interference with the particle counter's electronics. The Lasair® III particle counter has patented systems to reduce these effects as well as the effect of random particles within the cleanroom. Because random events cannot be interpreted in small number, statistical reviews have very little correlation to the general production activities; however they can be reviewed at a later stage when doing longer-term analysis of cleanroom performance. What is key is the consecutive or regular counting of low level of particulate that may give clues as to a possible contamination issue and should be investigated.

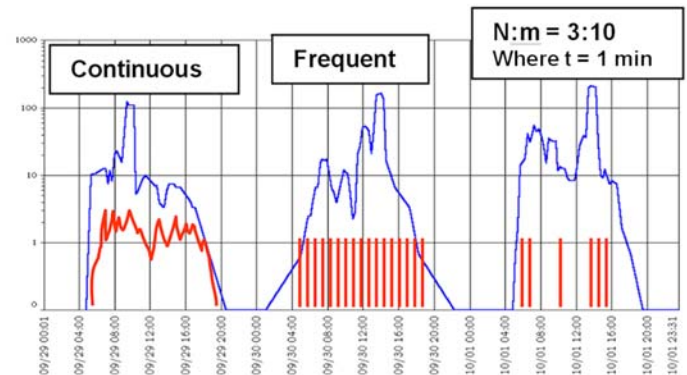


Figure 2. Daily Cleanroom Trend

Figure 2 shows three conditions:

Continuous: If continuous levels of 5.0 µm particles are seen in a cleanroom, an investigation should be undertaken, as it is unlikely that large particles would penetrate a filter. Therefore, the contamination is arising from a source that can be contained.

Frequent. When large particles occur with a frequency that is not random, then a source of these particles should be determined and where possible, rectified. The effect of the particles can be correlated against finished product testing to define what level of particle can be deemed a nuisance.

Random. When particles show no, or little, pattern of occurrence then a frequency of N of M should be

determined, i.e., no more than 3 particles in any 12 minutes – or similar. Again correlation back to finished product testing should validate the data used in routine monitoring.

The definition of the alert and alarm set points is also examined in the current GMP guidance:

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.

The determination of appropriate alerts means that proof of control over the environment, relative to product quality, should be maintained. Therefore, using the limits assigned by the certification data alone may not always be prudent. Rather, limits that better reflect the production environment of each particular facility, filling line, or similar should be determined.

Lyophilized Product

Product that has been filled aseptically and is to be freeze dried should be maintained within a Grade A environment from the point of stopper insertion to the freeze drier. If this is via a mobile cart, then this mobile environment must be shown to maintain a Grade A environment. When a stopper is not fully inserted, the vial is deemed to be open, and any aseptic vial open to the environment must be maintained within a controlled environment.

Once freeze drying is completed and the stopper pulled down into the vial or a mechanical pressure applied to ensure closure and the stopper is proven to be fully seated via a validated protocol, the vials should be maintained within a Grade A air supply until the cap is in place and crimped. Grade A environments are essentially ISO 14644-1 Grade 5 environments (see Table 1). Therefore, the quality of air being supplied to the crimping process is better described as being ISO 5 quality, from a particle perspective. If the capping activity is performed as an aseptic process, then a Grade A environment must be proven.

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