BECKMAN COULTER
Life Sciences

# GMP Cleanrooms Classification and Routine Environmental Monitoring

## Introduction

The various GMP guidelines and International ISO standards around GMP cleanrooms are complex and often appear to give conflicting advice, leading to confusion and sometimes incorrect interpretation. In the case of Routine Environmental Monitoring, there is very little prescriptive advice and the onus is on the cleanroom owner to devise an appropriate monitoring plan and, in the frequently prescriptive GMP industry, the lack of direct guidance leaves users struggling to know what to do and the temptation is to either create over-burdensome monitoring programs or to try to simply use the same monitoring plan as is used for classification. Both are incorrect: the first because over-burdensome monitoring programs can lead to more interventions in the critical cleanroom zones and the associated risk of contamination events; the second because Routine Environmental Monitoring programs should be based on a risk assessment of contamination threats to the product during the manufacturing process and the rules for Classification do not take this into account. For instance, the sampling locations for monitoring may be very different to those used in classifying the room itself once a risk assessment shows at what locations in the room the product is exposed to risk.

This paper discusses the differences between GMP Cleanroom Classification and Routine Environmental Monitoring and explains how Beckman Coulter can help.

## What is Cleanroom Classification?

Unlike Routine Environmental Monitoring, Cleanroom Classification is focussed on the cleanroom itself. If the user does not add additional sampling locations to those defined in ISO 14644-1:2015, the Classification does not take into account specific areas in the room where the manufacturing process or product may be at increased risk of contamination. It is a snapshot in time and, whilst it can be used to trend the cleanroom performance, the typical re-classification interval is annual, so the statistical validity of the data may be considered weak. Classification demonstrates that the cleanroom as a whole is in compliance with its intended air particle concentration class/limit at all points in the cleanroom.

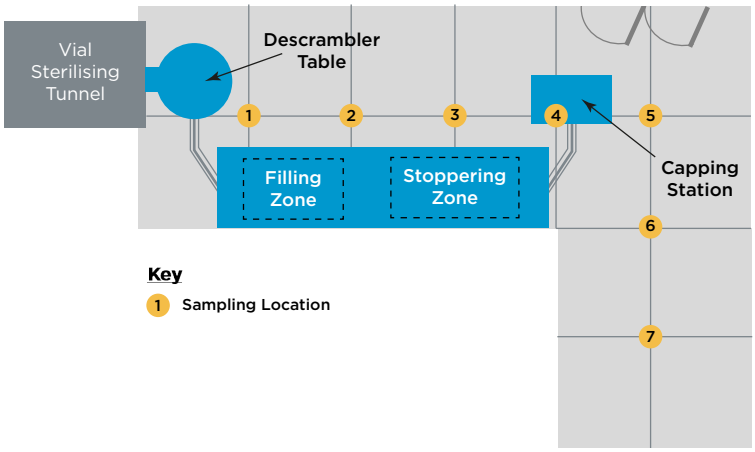


**Figure 1.** Cleanroom Classification to ISO 14644-1:2015 concentrates on the room performance, not risk to the product

Both EU GMP Annex 1:2009[1] and the FDA CGMP:2004[2] state that Classification is done to the method defined in ISO 14644-1:2015[3]. CGMP follows the maximum concentrations defined in ISO 14644-1:2015 for each of the cleanroom grades. GMP Annex 1 has its own particle limits, including a limit for 5 µm particles* for both classification and monitoring in Grade A, whereas ISO 14644-1:2015 does not define any limits for 5 µm particles in its equivalent to Grade A, ISO Class 5. (Note: the latest draft of the new GMP Annex 1[4] out for public comment at the time of writing this document does not ask the user to classify using both, but it does require the user to monitor for both 0.5 and 5 µm particle sizes during routine environmental monitoring programs.

### ISO 14644-1:2015:

i. uses a look-up table to define the number of sample locations required to classify a cleanroom

ii. states that the sampling locations should be distributed evenly across the cleanroom

iii. requires that the sample probe should be located at the same height as the work activity that takes place in that part of the cleanroom

iv. states that, where unidirectional airflow is provided, an isokinetic sample probe should be used and it should face towards the source of the airflow, i.e. into the oncoming stream of the unidirectional airflow

v. prescribes that the minimum sample volume taken at each location should be sufficient such that it could capture a minimum of 20 particles should that location be operating at the maximum allowable air particle concentration for its cleanroom Class, e.g., if the maximum number of air particles is
100/$m^3$, then a sample of 0.2 $m^3$ would be sufficient to capture 20 particles if the location were operating at the maximum allowable air particle concentration

vi. states that, if multiple samples are taken at each location, then the samples at that location should be averaged.

vii. Concludes that, should all locations have less than the maximum allowable air particle concentration for the target cleanroom class, then the cleanroom is deemed to have passed Classification.

### EU GMP Annex 1 calls for classification both at rest and in operation:

i. Cleanroom classification should be done at rest with no-one in the cleanroom and also in operation where the normal number of cleanroom staff are present and normal cleanroom activities are taking place, e.g. manufacturing.

### FDA CGMP emphasises the importance of classification in operation (CGMP uses the term "dynamic conditions"):

i. "It is important for area qualification and classification to place most emphasis on data generated under dynamic conditions (i.e., with personnel present, equipment in place, and operations ongoing). An adequate aseptic processing facility monitoring program also will assess conformance with specified clean area classifications under dynamic conditions on a routine basis."

## What is Routine Environmental Monitoring?

Unlike Classification, Routine Cleanroom Monitoring is undertaken daily for the critical zones and weekly for the less critical areas so the data can be used to trend the overall cleanroom contamination level over time. Sampling locations are focussed on monitoring the contamination risk at locations where the manufacturing process or product may be at increased risk of contamination. It is done to demonstrate both that the contamination risk areas are operating correctly prior to the start of manufacturing and also during the manufacturing itself.

Unlike Cleanroom Classification where the minimum number and location layout for the air particle sampling is well defined, the sample locations for Routine Monitoring are not fixed. Instead they

are specific to each individual process and to be determined by the process owner using a risk assessment, i.e. Routine Environmental Monitoring sampling should be done at locations which might put the product at risk from contamination. Examples which might put the product at risk are, but not limited to:

- filling zones
- hoppers for vial stoppers
- vial de-scrambler tables
- processing equipment,
- locations where there may be operator interventions

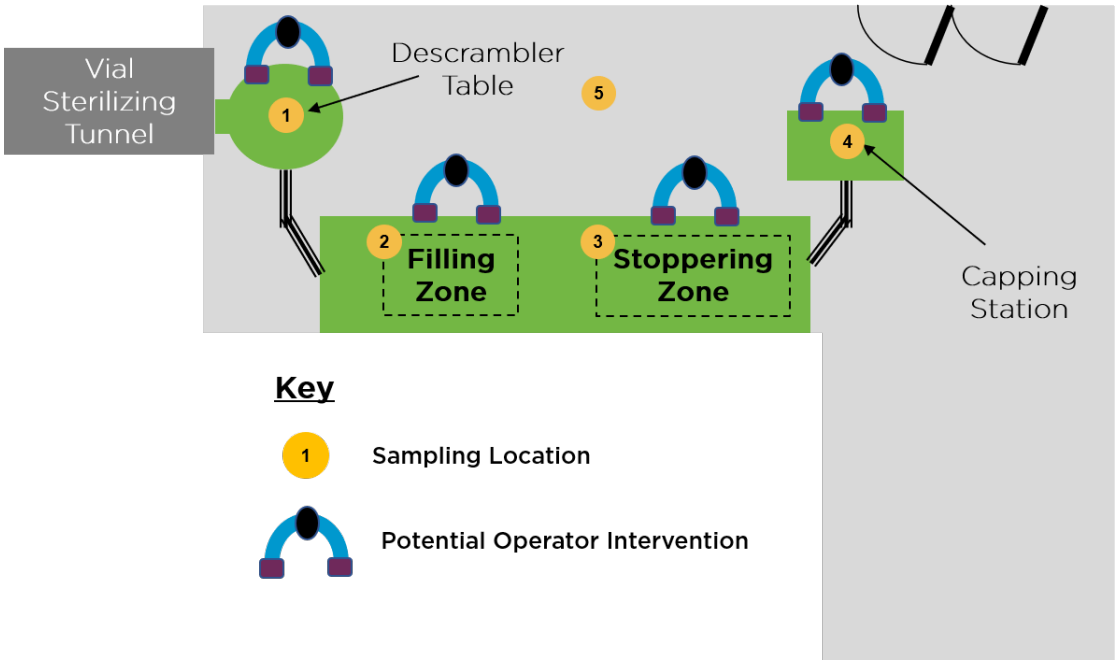


**Figure 2.** Routine Environmental Monitoring focusses on locations where the product may be at risk of contamination

Several risk assessment guides are available: two examples include: FDA Q9 Quality Risk Management Guidance Document[4] and the WHO Guidelines on Quality Risk Management TRS-981[5].

Here are some relevant excerpts regarding non-viable air particle counting from the FDA CGMP guidance:

i. "An adequate aseptic processing facility monitoring program also will assess conformance with specified clean area classifications under dynamic conditions on a routine basis."

ii. "Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 µm and larger when counted at representative locations normally not more than 1 foot (305 mm) away from the work site, within the airflow, and during filling/closing operations."

iii. "Regular monitoring should be performed during each production shift."

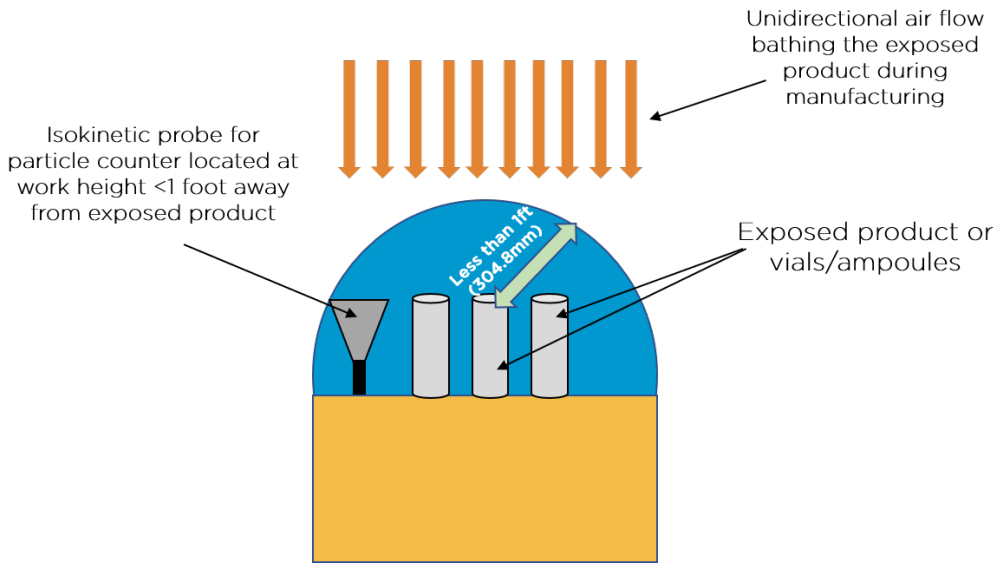


**Figure 3.** Routine Monitoring probe should be <1 ft (305 mm) away from exposed product

## Some relevant excerpts regarding non-viable air particle counting from the EU GMP guidance:

i. "Cleanrooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices."

ii. "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."

iii. "The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded."

iv. "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 ≥5.0 µm particle counts may 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."

## How can Beckman Coulter Life Sciences help?

Designing and validating your Cleanroom Routine Environmental Monitoring and Classification SOPs is time consuming and complex. MET ONE 3400+ portable air particle counters can help ensure that your SOPs are followed and minimise data errors by offering a level of automation to both processes:

### Electronic SOP Maps

- The sampling map, loaded into the counter as part of the SOP, guides users around their daily monitoring program.

### Interactive SOP Maps

- Onscreen instructions at each sample location tell technicians how and where to sample at each location. As each sample is completed, it turns green on the screen, showing users what remains to be done at a glance.

### Electronic SOP Version Control

- The Administrator manages SOP versions in the counter using electronic signatures. Updated SOPs are automatically replicated across all instruments.

### Review and Approve

- Once completed, results can be reviewed and approved in the counter remotely by the Supervisor using a web browser.

### Electronic Records

- Once approved, an electronic signature is attached to the final report which can then be exported in secure electronic format.

### Barcode function

- Connect a barcode reader to automatically capture sample location, or production batch ID, etc.

### 21 CFR Part 11

- MET ONE 3400+ uses Microsoft Active Directory for User Name and Password Control for log-on and electronic signatures.
- Each sampling record contains the SOP version number, the user name, the location name, time, date, alarms, counter configuration, sampling results and production batch ID.
- The database is secure and encrypted and the User does not have access to delete records.
- Secure electronic records can be exported straight from the counter.
- Administrator controls the versions of SOP inside the counter and signs-off new versions using electronic signatures.
- Filter Audit Trail by user, alert level exceeded, failed logins, etc. to quickly provide reports during audits.


**Figure 4.** MET ONE 3400+ allows users to create version-controlled interactive SOP sampling maps inside the counter itself, which instruct technicians where to sample, how to arrange the sampling probe at each location and indicates once sampling at each location is complete and allows the supervisor to remotely review and approve the day's monitoring records remotely via web-browser

## Conclusion

Non-viable air particle GMP Cleanroom Classification and Routine Environmental Monitoring are two very different processes: Classification is to determine that the air quality of the room itself is performing better than the target class limits and is determined by ISO 14644-1, whereas Monitoring is to determine that the air quality is performing better than the target class limits in locations where product may be at risk as determined by a risk assessment. Both processes can be complex and adding a level of automation through the MET ONE 3400+ can help reduce the risk that incorrect SOPs are used, that the SOP is not followed correctly and that data errors through human error are minimised, whilst supporting the creation of reviewed and approved electronic records that are 21CFR part 11 ALCOA compliant.

## References


1. European Commission. EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice. Medicinal products for human and veterinary use, Annex 1: Manufacture of Sterile Medicinal Products, 14th February 2008. European Commission Enterprise and Industry Directorate-General, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium.

2. Food and Drug Administration. Guidance for industry. Sterile drug products produced by aseptic processing – current good manufacturing practice, 2004. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Office of Regulatory affairs (ORA) Division of Drug Information, HFD-240 Center for Drug Evaluation and Research Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857 USA

3. ISO 14644-1:2015 Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration. Viewed 19/3/2020: **https://www.iso.org/standard/53394.html**

4. Food and Drug Administration: Q9 Quality Risk Management Guidance Document; **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q9-quality-risk-management** viewed 15th May 2020

5. World Health Organisation: Guidelines on Quality Risk Management TRS-981; **https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf** viewed 15th May 2020





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