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Hasim's focus is on cleanroom design and management concepts, environmental monitoring systems, pharmaceutical manufacturing and regulatory concerns. Hasim is a founding chair of Cleanroom Technologies Society of Turkey (TTD), head of delegation to ISO TC209 – Cleanrooms and associated controlled environments – and technical expert to ISO TC209 WG3 – Test methods. He was recently appointed as honorary chair of the International Confederation of Contamination Control Societies, ICCCS.

Hasim is an active member of ISPE, IEST and PDA and holds a Bachelor of Science degree with high honors in Atmospheric Science and Meteorological Engineering from Istanbul Technical University.

Main feature

Creating, implementing and maintaining a monitoring plan based on Risk Assessment

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Abstract

Clean areas used for aseptic manufacturing of sterile medicinal products are subject to standards and guidelines to ensure quality of production and to minimize risks of particulate and microbiological contamination. In recent years, a proper monitoring plan with a risk-based approach has become a part of many standards and regulations such as ISO 14644-2:2015 and ICH Harmonized Guideline ICHQ9 Quality Risk Management. However it is also obvious that there is a lack of good application practices for proper monitoring plans that are based on risk assessment. This study provides information with an example of how to prepare a risk based monitoring plan incorporating risk assessment tools, current standards, regulations and guidelines.

Cleanroom monitoring

Cleanroom non-viable airborne particle monitoring is essential. Particles are significant because they can enter a product as an extraneous contaminant, and can also contaminate it biologically by acting as a vehicle for microorganisms. There are different particle monitoring systems with remote locations such as manifold systems and online monitoring systems. For manifold systems, the particle counter should be connected to the manifold unit which changes sampling locations at defined intervals such as per minute. Between each sample, there is a buffer time which allows the sampling pathway in the manifold and the particle counter to clean.

Thus sequential sampling manifold systems are not suitable for sterile pharmaceutical monitoring since monitoring should cover every sample location continuously without delay or interruption. However, unlike manifold systems, online monitoring systems have independent particle counters with isokinetic sampling probes in every critical location and particle monitoring can be undertaken for the full duration of critical processing, including equipment assembly, in every selected monitoring location without delay or interruption.

How to select locations for monitoring

For cleanroom classification, the minimum number of single sample locations is defined based on the table in the standard (ISO 14644-1:2015). The cleanroom should be divided into similar sized zones and the sampling locations should be selected to represent the characteristics of each zone.

By contrast, for cleanroom monitoring, sample locations should be selected based on a formal risk assessment. Each representative location should be defined and verified based on historical data, trends and production routines. These representative locations are normally not more than 30cms away from the work area and within the airflow. The FDA Aseptic processing guideline recommends that measurements to confirm air cleanliness in critical areas be taken at sites where there is most potential risk to the exposed sterilized product, the containers, and the closures. The particle counting probe should be placed in an orientation that has been demonstrated to provide a meaningful sample. Regular monitoring should be performed during each production shift. Non-viable particle monitoring should be conducted with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters.

For the selection of locations to be sampled, the main considerations are:

- Location(s) should be based on the risk in the activity,
- Microbial contamination affects risks in product quality,

- Potential microbiological growth areas during production,
- Product flow considerations,
- Personnel flow considerations,
- Locations based on nature of process (wet areas, transfers, personnel intervention points etc.),
- All locations where there is a possibility of operator intervention, for example access points to the Grade A environment,
- Original room classification studies, qualification studies and the rationales for previously used sampling/monitoring arrangements,
- Areas where there are normally no interventions, but sterile components/products are still potentially exposed to airborne particulate contamination due to abnormal interventions or for other reasons,
- The length of time that sterile components and/or products are exposed during processing: An example might be stoppers in a feed hopper. In this instance, there is little risk of intervention. However, the stoppers may well be sitting exposed in the hopper for some time, so that there is a potential for build-up of particulate contamination over time. It would therefore be good practice to sample air at this location to demonstrate continued compliance of the air quality being delivered to the components during the processing time.

Critical areas to be considered are:

- The point of fill
- Component hoppers
- Inspection hatches
- Descrambler tables
- Stopper and capping stations
- Loading of Freeze Driers
- Unloading of sterile components not protected by autoclave bags
- Interfaces between equipment and the Grade A area
- Isolator transfer devices
- Aseptic manipulations
- Operator intervention

Difference between classification and monitoring:

Even though both classification and monitoring target airborne particle counts, there are different parameters such as regulations, sampling intervals, location selection etc. Table 1 can help users to identify these differences.

Table 1: Classification and monitoring

	Classification	Monitoring
Standard or regulation	**ISO 14644-1:2015**	EU GMP Annex 1/PIC's, WHO, ISO14644-2:2015
Period	Periodic classification testing shall be undertaken **annually** in accordance with ISO 14644-1. This frequency can be extended based on risk assessment.	**Online/continuous** *Should be undertaken for the **full duration of critical processing**, including equipment assembly*
Number of sampling points and their locations	**Based on ISO 14644-1:2015 Table A.1** Derive the minimum number of sampling points, N_L, from Table A.1. Select within each section a sampling location considered to be representative of the characteristics of that section.	Based on **formal risk assessment** (ICH-Q9) There is no magical calculation. Focus on locations where the product is open such as turn table, filling location, stopperring, lyophizer loading, etc. Use risk tools listed in ISO 14644-2:2015 to define risk level.
Sample duration	**Sample duration(min)= V_s/Particle Counter Flow Rate** If result is less than 1 minute then the minimum should be 1 minute at each location, *The volume sampled at each location shall be at least 2 litres, with a minimum sampling time of 1 min for each sample at each location.*	**Online/continuous** *Should be undertaken for the **full duration of critical processing**, including equipment assembly*
Sample volume	**ISO 14544-1:2015** $V_S = \{\frac{20}{C_{n,m}}\} X\ 1000$ Where: V_s is the minimum single sample volume per location expressed in litres $C_{n,m}$ is the class limit (number of particles per cubic metre) for the largest considered particle size specified for the relevant class ***20*** is the number of particles that could be counted if the particle concentration were at the class limit	**Best option to get fast action** *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.*
Risk assessment method	**Cleanroom classification report**	**Alarm interface** *all interventions, transient events and any system deterioration are captured, and alarms triggered if alert limits are exceeded.*

Risk assessment method

Probability (likelihood)

An estimation of the probability of the risk occurring classified as:

- **Low:** The risk occurs once per year.
- **Medium:** The risk occurs once per month.
- **High:** The risk occurs once per week.

Severity (impact)

An estimation of how serious the consequence is if the risk occurs:

- **Low:** Minor consequence and the effect declines fast.
- **Medium:** Moderate consequence, the effect is short to medium.
- **High:** Serious consequences with long term effect and potential catacatastrophic effect in the short term.

Risk class

A combined estimation of the severity (impact) and probability (likelihood) enables the risk to be classified (see Figure 1).

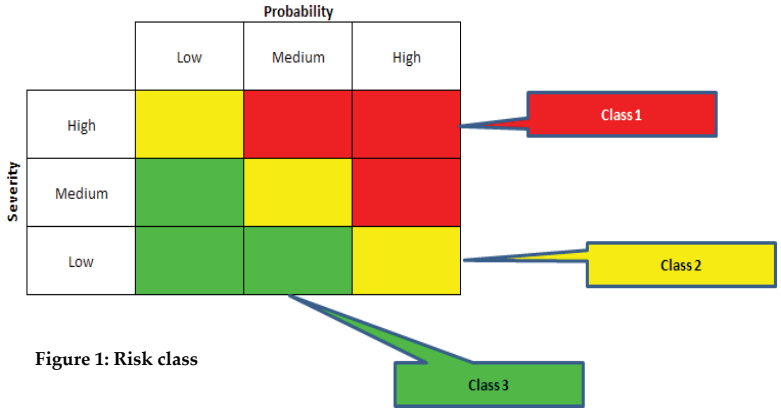

Figure 1: Risk class

Detectability

An estimation of the probability for a risk scenario to be discovered:

- **Low:** Low or less than one in three occurrences.
- **Medium:** Medium or about one in two occurrences.
- **High:** Likely to be discovered at every occurrence.

Priority

Prioritizing the risk scenarios allows better judgement of what measures are needed (see Figure 2):

- **Priority 1:** High priority means that the risk is high and that extended testing or possible system change should be carried out to minimize the risk.
- **Priority 2:** Medium priority means that testing at installation is recommended as well as the need for routine testing.
- **Priority 3:** Low priority means that
- some installation testing is recommended but routine testing is normally not necessary.

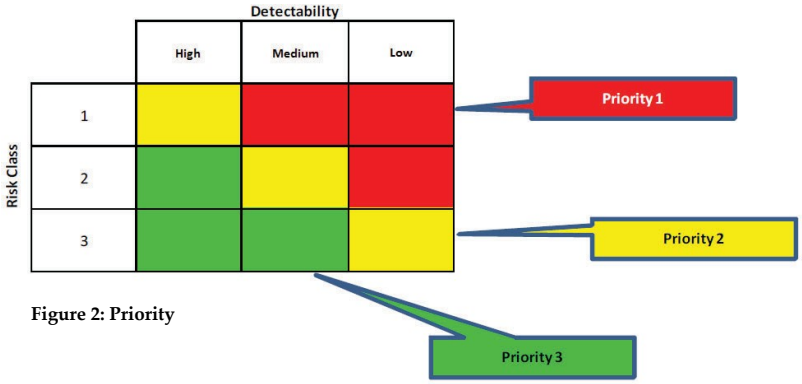

Figure 2: Priority

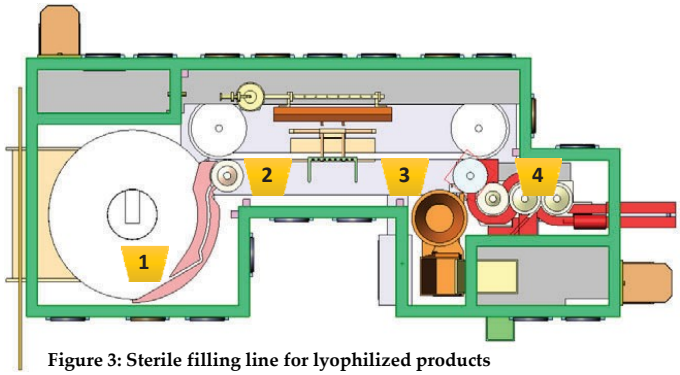

Figure 3: Sterile filling line for lyophilized products

Risk assessment example:

In the RABS sterile filling line for lyophilized products shown in Figure 3, there are over 100 potential locations for a non-viable sampling iso probe. However, considering product work flow, invasion points, operator interventions, the highest risk locations are considered to be:

1. **Tunnel exit:** All vials are open to ambient air under unidirectional airflow;
2. **Point of fill:** Area where the moving vials are filled with medicine by moving needles. Please note, probe locations are selected so as not to interfere with operator activities (e.g. gloved operations) and within 30cm of needle movement area.
3. **Stopper insertion:** Where vials stoppers are inserted to vials. In the example, stoppers are not fully closed due to the lyophilization process.
4. **Point of exit:** Exit point from filling where the semi-closed vials are transferred to the lyophilizer.

In this example, location 1, the tunnel exit, is considered.

Before installing a non-viable particle monitoring system to this RABS, a pre-risk study showed that the risk of particle contamination at location 1 was judged to be 'high probability' and 'high severity' and therefore a 'Class 1' risk (see Figure 1). The 'detectability' at that point was judged to be 'low' and the risk was therefore Priority 1 (see Figure 2).

After installation of the non-viable particle monitoring system, the post risk assessment showed that the risk of particle contamination at location 1 remained 'high probability' and 'high severity' and therefore a 'Class 1' risk (see Figure 1). In other words it was not possible to reduce the likelihood of particles at that point.
However, because the detectability increased to 'high' with the installation of the online non-viable particle monitoring system, the risk could be reduced to Priority 2 (medium).

The same methodology was applied to the other locations. Suitable forms are of course always used to document the pre-risk and post-risk studies in each location.