



Quality Risk Assessment for Environment Monitoring

INTRODUCTION:

Environmental Monitoring describes the microbiological testing undertaken in order to detect changing trends of microbial counts and micro-flora growth within cleanroom or controlled environments. The results obtained provide information about the physical construction of the room, the performance of the Heating, Ventilation, and Air-Conditioning (HVAC) system, personnel cleanliness, gowning practices, the equipment, and cleaning operations.

Over the past decade, environmental monitoring has become more sophisticated in moving from random sampling, using an imaginary grid over the room and testing in each grid, to the current focus on risk assessment and the use of risk assessment tools to determine the most appropriate methods for environmental monitoring.

This paper explores current trends in the application of risk assessment to the practice of environmental monitoring by examining the following key areas:

- Determining the Frequency of Monitoring: Using the concept of risk assessment to decide how often to monitor different types of cleanrooms
- Risk Assessment Tools: Applying risk assessment tools to establish methods for environmental monitoring
- Numerical Approaches: Considering a numerical approach to assess risk data using a case study of an aseptic filling operation

The examples used are from a sterile drug manufacturing facility and focus mostly on aseptic filling; however, the concepts and tools are applicable to the environmental monitoring of other types of manufacturing and packaging operations.

DETERMINING THE FREQUENCY OF MONITORING

In developing an adequate environmental monitoring programme, there should be a balance between using resources efficiently and monitoring at sufficiently frequent intervals so that a meaningful picture can be obtained. Sources of guidance with respect to monitoring frequencies are very limited within Europe, and the monitoring frequencies specified within the United States Pharmacopoeia (USP) <1116> may not be suitable for all facilities. Some guidance can be obtained from the International Organization for Standardization's (ISO) standards: principally ISO 14644 and ISO 14698. However, these do not always fit with regulatory guidance documents because they apply to controlled environments across a range of industries other than pharmaceuticals, where standards can be higher (Jahnke, 2001).

When establishing an environmental control programme, the frequency of monitoring different controlled areas can be determined based on 'criticality factors' relevant to each specific area.

Criticality Factors

The establishment of a criticality scheme on which to base monitoring frequencies is designed to target monitoring of critical process steps. Therefore, the final formulation process would receive more monitoring than an early manufacturing stage with a relatively closed process.

Using a criticality factor is a means of assigning a monitoring frequency based on the risk assessment of each critical area. The risk assessment relates to the potential product impact from any risk. For example, an area of open processing at an ambient temperature, a long exposure time, and the presence of water, would constitute a high risk and would attract a higher risk rating. In contrast, an area of closed processing, in a cold area, would carry a substantially lower risk and associated risk rating.

Using a range of 1 to 6, with '1' being the most critical and '6' the least critical, a score of 1 would be assigned to an



Quality Risk Assessment for Environment Monitoring

aseptic filling operation; a score of 2 to final formulation, a score of 3 to open processing, and so on. Each user must adapt such a scheme to his or her particular area and defend it by way of supportable rationale. An example of monitoring frequencies under such a scheme can be seen in *Figure 1*, and an example of its application is seen in *Figure 2*.

Figure 1

Criticality Factors of Monitoring Frequencies

Criticality Factor	Frequency of Monitoring
1	Daily or Each Batch
2	Weekly
3	Fortnightly or Bi-weekly
4	Monthly
5	Three-monthly or Quarterly
6	Six-monthly or Semi-annually

Each controlled area would be evaluated against set criteria and, with the use of a series of guiding questions, the monitoring frequency would be determined. Decision criteria include considerations in two category areas: areas of higher weighting and areas of higher monitoring frequency. Examples of these categories follow:

Giving Higher Weighting to –

- ‘Dirtier’ activity performed in a room adjacent to a clean activity, even if the clean activity represents later processing
- Areas that have a higher level of personnel transit (given that people are the main microbiological contamination source). This may include corridors and changing rooms.
- Routes of transfer
- Areas that receive in-coming goods
- Component preparation activities and sites Duration of activity (such as a lower criticality for a 30-minute process compared to a six-hour operation)

Having Higher Monitoring Frequencies for –

- Warm or ambient areas as opposed to cold rooms
- Areas with water or sinks as opposed to dry, ambient areas
- Open processing or open plant assembly compared to processing that is open momentarily or to closed processing (where product risk exposure time is examined)
- Final formulation, purification, secondary packaging, product filling, etc.



Quality Risk Assessment for Environment Monitoring

Figure 2

Application of Criticality Factors

Environmental Criticality Factor	Likelihood of Environmental Impact on Finished Product	Definition	Monitoring Frequency
1	Highly Likely	Aseptic filling where no further processing takes place. Here the risk of contamination would have a considerable product impact because contaminants could not be reduced or removed by further processing.	Daily or Each Batch
2	Likely	Area of final formulation. This may apply to an area where the final process is a sterilizing grade filter.	Weekly
3	Moderately Likely	Direct or indirect exposure of the product to the environment is somewhat likely to introduce contaminants. This may also apply to an area that is at ambient temperature and where there is a high water presence.	Fortnightly or Bi-Weekly
4	Unlikely	This may apply to cold areas where little or no open processing takes place.	Monthly
5	Very Unlikely	Indirect exposure to the environment is highly unlikely to introduce contaminants that could affect the finished product. If a contaminant were to be introduced, sufficient downstream controls and/or the use of preservative agents are highly likely to remove and significantly reduce contaminants.	Every 3 Months or Quarterly
6	High Unlikely	An area that is uncontrolled or where microbial contamination is very unlikely, such as a freezer.	Every 6 Months or Semi-annually

Once the monitoring frequency for each controlled area is determined, it should be reviewed at regular intervals. This review may invoke changes to a room's status, and hence, its monitoring frequency, or to changes for different sample types within the room. For example, it may be that after reviewing data for one year, surface samples produce higher results than air samples for a series of rooms. In this event, the microbiologist may opt to vary the frequency of monitoring and take surface samples more often than air samples. There would also be an increased focus on cleaning



Quality Risk Assessment for Environment Monitoring

and disinfection practices, and their frequencies, based on such data (Sandle, 2004b).

When both types of monitoring are producing low level counts, the balance of risk would be towards air samples. This is because air samples are direct indicators of the quality of the process and assign a level of control to the process, whereas surface samples are indicators of cleaning and disinfection. If the results of surface samples are generally satisfactory, as indicated by trend analysis, then either the number of samples or the frequency at which they are taken can be reduced. If subsequent data showed an increase in counts, the monitoring frequency could easily be restored. Indeed, all types of monitoring frequencies may increase as part of an investigation, as appropriate. Therefore, the criticality factor approach not only sets the requirement for a room, it can also be used to vary the sample types within a room (Ljungqvist and Reinmuller, 1996).

RISK ASSESSMENT TOOLS

Once the status for each room has been selected, a risk assessment procedure is required to determine locations for environmental monitoring. Such risk-based approaches are recommended in ISO 14698 and regulatory authorities are increasingly asking drug manufacturers about this subject.

Risk-based approaches include Failure Mode and Effects Analysis (FMEA), Fault Tree Analysis (FTA), and Hazard Analysis and Critical Control Points (HACCP), all of which employ a scoring approach. (Other approaches include: Failure Mode, Effects, and Criticality Analysis (FMECA); Hazard Operability Analysis (HAZOP); Quantitative Microbiological Risk Assessment (QMRA); Modular Process Risk Model (MPRM); System Risk Analysis (SRA); Method for Limitation of Risks; and Risk Profiling.)

At present, no definitive method exists, and the various approaches differ in their process and in the degree of complexity involved. However, the two most commonly used methods appear to be HACCP, which originated in the food industry, and FMEA, which was developed for the engineering industry (Whyte and Eaton, 2004a).

These various analytical tools are similar in that they involve:

- Constructing diagrams of work flows
- Pin-pointing areas of greatest risk
- Examining potential sources of contamination
- Deciding on the most appropriate sample methods
- Helping to establish alert and action levels
- Taking into account changes to the work process and seasonal activities

These risk assessment approaches are not only concerned with selecting environmental monitoring locations. They integrate the environmental monitoring system with a complete review of operations within the cleanroom to ensure those facilities, operations, and practices are also satisfactory. The approaches recognise a risk, rate the level of the risk, and then set out a plan to minimise, control, and monitor the risk. The monitoring of the risk will help to determine the frequency, locations for, and level of environmental monitoring (for example, refer to an article by Sandle [2003a], for a more detailed example).

This paper explores an example from three different techniques:

- A simple conceptualisation of risk using a table
- HACCP
- FMEA



Quality Risk Assessment for Environment Monitoring

Tabular Approach

An example using a simple table for analyzing risk in environmental monitoring situations appears in *Figure 3*.

Figure 3

Tabular Approach to Risk Assessment

Area or Equipment: Sterility Testing Isolator		
Risk: Contamination due to build-up of microbial counts in the isolator environment		
Failure or Situation: Failure to adequately clean after use		
Effect	Minimising the Risk (Mitigations to Reduce Risk)	Monitoring
<ul style="list-style-type: none"> • When isolators are not cleaned regularly, there is a possibility of micro-organisms remaining in the environment. 	<ul style="list-style-type: none"> • Cleaning surfaces using water to remove dirt or spillages prior to the application of a suitable disinfectant. • The disinfectant used must have a wide spectrum of efficacy, but not be aggressive to the isolator material. • The isolator should be designed so that it is easy to clean. 	<ul style="list-style-type: none"> • An environmental monitoring programme (using settle plates, air samples, contact plates, swabs, or finger plates) will show the areas of greatest risk. This data should be examined for trends. • For out-of-limits environmental monitoring results, appropriate Corrective and Preventive Actions (CAPA) should be put in place.

HACCP

- The seven principles behind constructing an HACCP analysis consist of:
 1. Identifying hazards or contamination risks and assessing their severity
 2. Determining Critical Control Points (CCPs)
 3. Establishing critical limits
 4. Establishing a system to monitor and control CCPs
 5. Establishing corrective action when a CCP is not under control
 6. Establishing procedures for verification to confirm that the HACCP system is working effectively
 7. Establishing documentation and reporting systems for all procedures

Each of these seven key points is a vital step in developing the risk assessment.

- The seven points include:
 1. Construct a risk diagram, or diagrams, to identify sources of contamination. Diagrams should show sources and routes of contamination.
Examples include:
 - Areas adjacent to Cleanroom or Isolator (e.g.: airlocks, changing rooms)
 - Air supply and Room air



Quality Risk Assessment for Environment Monitoring

- Surfaces
 - People Machines and Equipment
2. Assess the importance of these sources and determine whether or not they are hazards that should be controlled.
Examples include:
- Amounts of contamination on, or in, the source that is available for transfer
 - Ease by which the contamination is dispersed or transferred
 - Proximity of the source to the critical point where the product is exposed
 - Ease with which the contamination can pass through the control method
- The use of a scoring method can greatly help in assessing the relative importance of these contamination sources.
3. Identify the methods that can be used to control these hazards.
For example:
- Air Supply: High Efficiency Particulate Air (HEPA) filters
 - Dirty Areas adjacent to Cleanroom or Isolator: differential pressures, airflow movement
 - Room Air: air change rates, use of barriers
 - Surfaces: sterilisation, effectiveness of cleaning and disinfection procedures
 - People: cleanroom clothing and gloves, room ventilation, training
 - Machines and Equipment: sterilisation, effectiveness of cleaning, exhaust systems
4. Determine valid sampling methods to monitor either the hazards or their control methods or both.
For example:
- HEPA filter integrity tests
 - Air supply velocity, air change rates
 - Room pressure differentials
 - Particle counts
 - Air samplers, settle plates, contact plates, etc
5. Establish a monitoring schedule with 'alert' and 'action' levels and the corrective measures to be taken when these levels are exceeded.
For example:
- The greater the hazard, the greater the amount of monitoring required
 - Trend analysis for alert and action levels, in or out of control
6. Verify that the contamination control system is working effectively by reviewing key targets like product rejection rate, sampling results, control methods, and so on. These may require modification over time.
For example:
- System for data review
 - Examine filling trials
 - Audits
 - Reassess - hazards, effectiveness of control systems, frequency of monitoring, appropriateness of alert and action levels
7. Establish and maintain documentation.
For example:
- Describe the steps being taken
 - Describe the monitoring procedures
 - Describe the reporting and review procedures

Before implementing HACCP, it is important to train all staff involved in the process and to use a multi-disciplinary team. For example, the team may be comprised of personnel from Production, Engineering, Quality Control (QC), Quality Assurance (QA), Validation, and so on.

FMEA



Quality Risk Assessment for Environment Monitoring

FMEA schemes vary in their approach, scoring, and categorisation. All methods share a numerical approach. The example presented here, based on a sterility testing isolator, assigns a score (from 1 to 5) to each of the following categories:

- Severity
- Occurrence
- Detection

Where:

- Severity is the consequence of a failure
- Occurrence is the likelihood of the failure happening based on past experience
- Detection is based on the monitoring systems in place and on how likely a failure can be detected

By asking a series of questions, each main part of the cleanroom or isolator system can be grouped or classified into key parts.

Such questions include:

- What is the function of the equipment? What are its performance requirements?
- How can it fail to fulfil these functions?
- What can cause each failure?
- What happens when each failure occurs?
- How much does each failure matter? What are its consequences?
- What can be done to predict or prevent each failure?
- What should be done if a suitable proactive task cannot be found?

The scoring is 1 (very good) to 5 (very bad). Therefore, a likelihood of high severity would be rated 5; high occurrence rated 5; but a good detection system would be rated 1.

Using these criteria, a final FMEA score is produced from:

Severity score x Occurrence score x Detection score

Decisions on further action will depend upon the score produced. There is no published guidance on what the score that dictates some form of action should be. However, 27 is the suggested score for the cut-off value at which action is required. This is based on 27 being the score derived when the mid-score is applied to all three categories (i.e., the numerical value '3' for severity 3 x occurrence 3 x detection 3) and the supposition that if the mid-rating (or a higher number) is scored for all three categories, then at a minimum, the system should be examined in greater detail.



Quality Risk Assessment for Environment Monitoring

Figure 4

Isolator Operation Example

An example of one area of an isolator operation, and the risks associated with the room in which the isolator is housed, is examined below.

Description of the Critical Area: The isolator is situated in an unclassified room. There is no requirement to place a sterility testing isolator in a classified room.

FMEA Schematic:

Process Step	Failure Mode	Significance of Failure	Severity of Consequence (score)
Loading isolators pre-sanitisation, performing sterility testing	That contamination from the room could enter transfer or main isolators	Reduced efficiency of transfer isolator sanitisation, contamination inside main isolator	3

Measures to Detect Failure	Occurrence (score)	Detection Systems	Detection (score)
Would be shown from reduced evaporation rate for isolator sanitisation, poor environmental monitoring results in main isolator, potential sterility test failures. Sanitisation cycle has been validated using biological indicators of 10 ⁶ spores.	1	Isolator room is monitored monthly for viables and particles, staff wear over-shoes on entry, Dycem mat in place, entry to room has controlled access, environmental monitoring performed inside main isolator. Isolators are at positive pressure to the room, and air is HEPA filtered.	1

FMEA score: 3 x 1 x 1 = 3

Analysis: There is no problem to be considered from the room environment described. Entry to the room is controlled; the sanitisation cycle has been challenged with a level of micro-organisms far greater than would ever be found in the environment (spores of *Geobacillus stearothermophilus*); all items entering the isolator are sanitised (using a chlorine dioxide-based sporicidal disinfectant); and the isolator itself is an effective, positive pressure barrier to the outside (at >15 pascals).

As detailed earlier, environmental monitoring is performed inside the isolator during testing. This monitoring, which has an action level of 1 CFU (Colony Forming Unit), is designed to detect any potential contamination inside the isolator environment.



Quality Risk Assessment for Environment Monitoring

NUMERICAL APPROACHES

A third component of the risk assessment approach is to evaluate a risk once an activity has taken place. Then, by using a largely numerically-driven set of tools, repeatability and reproducibility can be ensured. Examples of individual out-of-limits results and data-sets relating to an operation are examined below using examples from an aseptic filling process. Following this, an example of an overall assessment of different processes over time is explored. Numerical approaches are useful in applying a level of consistency between one decision and another.

Individual Assessments

The section below details some methods that can be used to quantify the risk of contamination in pharmaceutical cleanrooms. The models outlined are based on the work performed by Whyte and Eaton (2003a and b).

- Estimating the Risk to Product Using Settle Plate Counts

The method applies to the assessment of settle plates at the point-of-fill, under the Grade A zone. It allows an estimate of the probable contamination rate to the product as derived from the following equation:

$$\begin{aligned} \text{Contamination rate (\%)} &= \\ &\text{Settle plate count} \quad \times \\ &\frac{\text{Area of product}}{\text{Area of petri dish}} \quad \times \\ &\frac{\text{Time product exposed}}{\text{Time settle plates exposed}} \quad \times 100 \end{aligned}$$

The fixed value is the area of the petri dish, which for a 90mm plate, is 64 cm².

- Settle Plate Count Worked Example:
 - Area of petri dish = 64 cm²
 - Settle plate count = 1 cfu
 - Neck area of product = 1 cm²
 - Exposure time of product = 1 minute
 - Exposure time of settle plate = 240 minutes

By inserting these example values into the equation:

$$\frac{1 \times 1 \times 1}{64 \times 240} = 0.000065 \times 100 = 0.0065\%$$

The formula can also be applied to the monitoring of product filtration activities when '1' is entered as a constant for neck area of product.

There is no available guide as to what percentage constitutes which level of risk. The 0.03% figure has been used by some practitioners. This is based on the Parenteral Drug Association Survey of Aseptic Filling Practices (2002), where it is common in the pharmaceutical industry to allow 0.03% of broth bottles in a media simulation trial to exhibit growth



Quality Risk Assessment for Environment Monitoring

at a 'warning level' (where 0.03% = 1/3,000, with 3,000 being the average size of a media fill). An 'action level' is often set as 3/3,000 bottles or 0.1%. This would constitute a high risk. Logically, the range between 0.03 and 0.1 would be a medium risk (Whyte and Eaton, 2004c).

Therefore, where the 'risk' is that of micro-organisms detected on a settle plate, with a probability of <0.1% depositing in the neck of a bottle when bottles are exposed in a unidirectional air flow, risk categories would be as shown in *Figure 5*.

Figure 5

Micro-Organism Risk Categories

Percentage	Risk
<0.03%	Low
>0.03 – 0.09%	Medium
≥0.1%	High

Finger Plate Assessment

The formula can readily be applied to operations that relate to Grade A operations, for example: filtration connection, vessel to filling machine connection, the filling activity, and loading a freeze-dryer. Where the operator is only present in the Grade B room and has no impact on the Grade A operation, this is automatically considered to be low risk if there are no other special factors. (Low risk does not imply lack of action or assessment. However, it aims conceptualisation of the result in terms of probable risk to the batch.)

The following formula can be used:

**Microbial count x Location x Method of intervention x
Duration of operation**

Where:

Microbial Count	=	Count in cfu for the plate
Location	=	Area of the filling machine, or other location to which the plate relates
Activity	=	Whether the hand directly touched part of the filling machine or if utensils were used
Duration	=	Length of the activity in seconds

In this example of a finger plate assessment, the location, activities, and duration require weighting. Examples of logic



Quality Risk Assessment for Environment Monitoring

that apply to the rating of the location, activities, and duration categories can be seen in *Figures 6, 7, and 8*, respectively

Figure 6

Weighting Location Example

Location	Rating*	Reason
General part of machine not close to filling zone	0.5	Data from air flow patterns suggests very low risk of contamination movement into the unidirectional air stream over the filling zone
Off-load	0.5	Off-load areas are present for all filling machines. The bottles and vials are partially stoppered and utensils are normally used. The likelihood of contamination is considered to be low.
On-load	1.0	On-load areas are present for all filling machines. The bottles and vials are not stoppered, although utensils are normally used. The likelihood of contamination is higher than for off-load.
Stopper bowl	1.5	Stopper bowls are present for filling machines. A direct intervention into the bowl could result in micro-organisms being deposited onto stoppers. The risk of this is considered higher than the risk with on-load or off-load activities, although such an intervention is rare.
Freeze-dryer loading	1.5	This is a direct intervention Grade A activity. However, vials and bottles are partially stoppered and are contained with cassettes.
Point-of-fill: air sample placement	2.0	The placement of an air sampler does not involve the touching of any filling equipment (such as needles, balances etc.). However, as a direct intervention into the Grade A zone, it is a higher risk than those parts of the filling machine previously examined.
Filtration transfer	2.0	The connection of a vessel for the purpose of transferring a product into the Aseptic Filling Suite requires human intervention and aseptic technique. If this process becomes contaminated, this could affect the product. The time taken to perform the connection is normally very short (under 30 seconds), which reduces the risk.
Machine connection	2.5	The connection of a vessel to the filling machine requires human intervention and aseptic technique. If the transfer line is contaminated, this could cause contamination to the product.
Point-of-fill: intervention	2.5	A direct intervention, where for example, filling needles are re-adjusted, is the highest risk rating. Counts associated with such activities require detailed examination.



Quality Risk Assessment for Environment Monitoring

Figure 7

Weighting Activities Example

Activity Method	Rating	Reason
Using forceps	0.5	The operative does not directly touch the machine and the utensils used are sterile.
Hand	1.0	The operative directly touches the machine, thereby creating a greater risk. However, it is procedure to sanitise hands prior to undertaking the operation.

Figure 8

Weighting Duration Example

Duration	Rating	Reason
Less than 30 seconds	0.5	The length of the intervention is considered minimal.
30 seconds - 120 seconds	1.0	The intervention is at the average* time taken.
Plus 120 seconds	1.5	The intervention has taken longer than average*.

* Based on the average time taken for media simulation trials, based on data from a UK pharmaceutical facility.

Finger Plate Assessment Worked Example

A finger plate with a count of 1 cfu for an activity at point-of-fill, using forceps, that lasts for one minute.

Microbial count x Location x Method of intervention x Duration of operation

$$1 \times 2.5 \times 0.5 \times 1 = 1.25$$

The score produced would be rated according to standard risk assessment categories:

Score	Risk
1 - 3	Low
4 - 8	Medium
9+	High

These risk ratings are based, in part, on the worked example. Based on historical data over the past six-months, the highest record example of a Grade A intervention finger plate is a count of 2 cfu: using forceps to retrieve a fallen vial and lasting for more than 120 seconds. This would have given a score of 7.5, which falls within the medium risk



Quality Risk Assessment for Environment Monitoring

category. The user should develop a scheme that fits his or her facility (Whyte and Eaton, 2004b).

Surface Sample Assessment

The following formula can be applied to filling and filtration activities:

Microbial count x Risk Factor A x Risk Factor B x Risk Factor C

Where:

Risk Factor A = Proximity to critical area

Risk Factor B = Ease of dispersion of micro-organisms

Risk Factor C = Effectiveness of control measure

Samples are taken using contact plates and swabs and are all post-operation.

- The following approach can be used in setting the risk factors:
 - The first step is to assign the risk (A) factor based on proximity of location to the critical area (filled product). The logic demonstrated in *Figure 9* may be used to determine risk factor A.

Figure 9

Determining Risk Factor A

Manufacturing Stage/ Location	Risk Factor (A)	Reason
Filtration room product contact	2.0	Samples of the transfer line may indicate potential for contamination to affect product.
General filling room or filtration room area (Grade B)	0.5	The samples reflect room cleanliness and general trends only. The impact upon the Grade A activity is low - unless the same micro-organism has been detected from a Grade B action level sample. In this event, the risk factor increases to 1.
Machine general (non-product contact)	1.0	Samples indicate state of general machine cleanliness but, the risk of exposure of product to contaminant is low - unless the same micro-organism has been detected from a Grade B action level sample. In this event, the risk factor increases to 2.5.
Machine product contact site	2.5	Sites include utensils, filling needles, and stopper bowls. Direct contact with product: highest risk.

- » The second step is to assign a risk factor (B) based on ease of dispersion or transfer of micro-organisms. See *Figure 10* for an example of the reasoning that would support Risk Factor B.



Quality Risk Assessment for Environment Monitoring

Figure 10

Determining Risk Factor B

Manufacturing Stage/ Location	Risk Factor (B)	Reason
Filtration room product contact	0.5	Connection is a short activity (less than thirty seconds) performed under Grade A Uni-Directional Air Flow (UDAF) protection; operator wears sanitised gloves.
General filling room or filtration room area (Grade B)	1.0	Periphery to the Grade A zone. Risk of transfer is low. Risk rating would increase to 1.5 if a Grade A and a Grade B sample exceeded action level and was characterised as the same microbial species.
Machine general (non-product contact)	1.5	Location is within the critical area, but not directly in product contact area. Some risk of transfer exists, but protective measures should prevent this.
Machine product contact site	2.5	Sites include utensils, filling needles, and stopper bowls that are directly within the critical zone. Direct contact with product: highest risk.

- » The third step is to weight the risk factor 'C' by assessing the effectiveness of the control measure. See Figure 11 for an example of this assessment.

Figure 11

Determining Risk Factor C

Manufacturing Stage/ Location	Risk Factor (C)	Reason
Filtration room product contact	0.5	Grade A UDAF and sterilised components; operator wears two pairs of gloves and sanitises hands.
General filling room or filtration room area (Grade B)	0.5	Floor is sanitised. Barrier exists by way of filling machine doors and UDAF.
Machine general (non-product contact)	1.0	Sterilised machine components; lines are wiped with disinfectants; UDAF protection.
Machine product contact site	1.5	Sterilised machine components; no direct intervention; UDAF protection; however, site is in direct contact with product.

Surface Sample Worked Example:

Where a count of 2 is detected from a conveyor belt (a filling machine non-product contact location)

Using the formula:



Quality Risk Assessment for Environment Monitoring

Microbial count x Risk Factor A x Risk Factor B x Risk Factor C
2 x 1 x 1.5 x 1 = 3

Risks can be scored against standard risk assessment categories:

Score	Risk
1 - 3	Low
4 - 8	Medium
9+	High

This scoring scheme is based on contamination of a product contact site being high risk by virtue of its direct proximity to the critical area or the product.

A count of 1 cfu on one of these product contact site locations would give a score of 9.4. In most filling zones and clean zones, sample results from product contact sites would be expected to record zero counts for 999 samples out of every 1000. Whereas, a count of 3 from a non-product contact site would result in a medium risk category.

Air Sample Assessment

Approaches are available for the risk assessment of active air samples that use a numerical system. However, the formulae associated with these are difficult to calculate in practice because often all information is not available and assessment of variables, such as impaction speed, are not readily calculable. Therefore, a qualitative assessment, such as the one included in the example of the numerical approach, may be more suitable.

An example of the numerical approach:

Airborne microbial count (cfu /m3) x deposition velocity of micro-organisms from air (cm/s) x area of product exposed (cm2) x time of exposure (s)

Alternatively, non-numerical risk assessment can be used based on the proximity and the operation. See *Figure 12* for this example.



Quality Risk Assessment for Environment Monitoring

Figure 12

Non-Numerical Risk Assessment Example

Activity, Area, Proximity	Risk	Reason
General room environment during filling or filtration, away from Grade A zone	Low	Provided there are no Grade A interventions and there are no counts recorded at Grade A, where counts are recorded at Grade A and there is a micro-organism match, then the category is re-defined as medium risk
Grade A, near critical zone	Medium	Close, but not at the point-of-fill
Grade A point-of-fill at critical zone	High	At point-of-fill

Note: Where growth is detected on the operator who placed the air sampler at Grade A, and this is shown to be the same micro-organism, the category of risk is increased by one (i.e.: low becomes medium and medium becomes high).

Assigning a Risk Factor to Areas of the Filling Room

The location where a high bio-burden is isolated within the filling area is arguably of greater consequence than the actual count. The location can be given a risk rating in relation to its proximity to the critical zone, ease of dispersion or transfer, and effectiveness of control methods.

The table shown in *Figure 13* is proposed as a tool for risk assessment and to aid investigations. It supplements the risk assessment tools that have been previously examined.



Quality Risk Assessment for Environment Monitoring

Figure 13

Filling Room Risk Assessment Example

Ease of Dispersion or Transfer of Micro-organisms	Proximity or Location of Source from Critical Area	Effectiveness of Control Method
None	None	None
Very low, e.g.: fixed place on sterilised area	Low, e.g.: at extreme limit of room away from filling zone	Low, e.g.: barrier control; UDAF
Medium, e.g.: product contact device	Medium, e.g.: general area of cleanroom near filling machine or at edges of Grade A zone	Medium, e.g.: sanitisation
High, e.g.: gloved hands of operators with direct contact with product	High, e.g.: within the critical area	High, e.g.: no effective controls

The type of product and whether further processing occurs can also influence the risk factors. See Figure 14 for an example. In considering batches with a high risk rating, further processing of the product can be considered and ranked (1 = lowest risk, 4 = highest risk).

Figure 14

Product-related Risk Assessment Factors

Product	Rank	Reason
Freeze-dried	1	Freeze-drying will destroy most micro-organisms
Liquid product, heat treated	2	Undergoes pasteurisation - effective against most non spore-forming micro-organisms
Intra-muscular product	3	Small volume; intra-muscular route
Intravenous product, no further treatment	4	Intravenous route; no further processing

An Overall Assessment

The approach taken for an overall assessment involves the historical examination of a number of operations and assigning a value above which the operation is considered to be atypical. A 95% cut-off is considered to be the most suitable cut-off point.

CRITICALITY SCORING

Criticality scoring is a way of assessing the totality of results from an environmental monitoring session. This may be, for example, a batch fill. The data from the session is examined and points are awarded for each result above a pre-set warning or action level. The total score is then summed and the results obtained are compared to a set level at which



Quality Risk Assessment for Environment Monitoring

atypical sessions are indicated.

The pre-set level would be assessed from historical data over a reasonable time period (such as one year). An example of such a scheme follows:

For Grade A

The results from a filling operation are examined (for individual viable counts and for the mean particle counts taken during the fill). Each result, which equals or exceeds a warning or action level, is scored according to the criteria in *Figure 15* and *Figure 16*. Using the criteria presented in *Figures 15 and 16* produces the Grade A score.

Figure 15

Viable Counts Criteria for Grade A

Sample	Count (cfu)	
	Warning Level	Action Level
Active Air Sample	5 points	10 points
Settle Plate	5 points	10 points
Contact Plate	5 points	10 points
Swab	5 points	10 points
Finger Plate	5 points	10 points

Figure 16

Particle Count Criteria for Grade A

Particle Size	Count (cfu)	
	Mean Counts from fill at Warning Level	Mean Counts from fill at Action Level
0.5 m	5 points	10 points
5.0 m	5 points	10 points

For Grade B

The results from a filling operation are examined (for the individual viable counts and the mean particle counts taken during the fill). Each result that equals or exceeds a warning level is scored according to the criteria in *Figure 17* and *Figure 18*.



Quality Risk Assessment for Environment Monitoring

Figure 17

Viable Counts Criteria for Grade B

Sample	Count				
	1 cfu	2-3 cfu	4-5 cfu	Warning Level	Action Level
Active Air Sample	1 point	2 points	3 points	3 points	5 points
Settle Plate	1 point	2 points	3 points	3 points	5 points
Contact Plate	1 point	2 points	3 points	3 points	5 points
Swab	1 point	2 points	3 points	3 points	5 points
Finger Plate	1 point	2 points	3 points	3 points	5 points

Figure 18

Particle Count Criteria for Grade B

Particle Size	Count (c/cf)	
	Mean Counts from fill at Warning Level	Mean Counts from fill at Action Level
0.5 m	4 points	5 points
5.0 m	4 points	5 points

If a warning level or action level is of the same count (cfu) as a value in the count (cfu) column, the warning or action level score should be selected. This produces the Grade B score. To produce the total criticality score, the two scores are added together (Grade A + Grade B).

Once the data has been generated, the score at which approximately 95% of the fills would be below (and 5% would be above) can be calculated. That figure would then be used as the cut-off value with which to assess the 'atypical' filling operations.

Figure 19 displays a simple representation of this assessment. For the data set, the criticality score was calculated at 25, which corresponded with the 95th percentile for a set of data from the filling of an example drug.

The graph in Figure 19 indicates that some fills exceeded the cut-off criticality value during a particular time period (see fill numbers 12 through 15). After some corrective action, the scores for the fills were reduced (see fill numbers 16 through 29) and the situation returned to a state of control.

CONCLUSION

The use of risk assessment approaches is an important current Good Manufacturing Practice (cGMP) topic in microbiological environmental monitoring. This paper has outlined some possible tools for such a risk assessment approach; however, each suite of cleanrooms or isolator will be subtly different. The microbiologist must consider each aspect of the environment and decide what level of monitoring best suits his or her system, and then must justify the techniques used and the locations selected.

The approach adopted should be detailed in a written rationale and approved by senior management. After this, a rigorous and defensible system will be in place to satisfy regulatory expectations, and to aid the user in assessing the

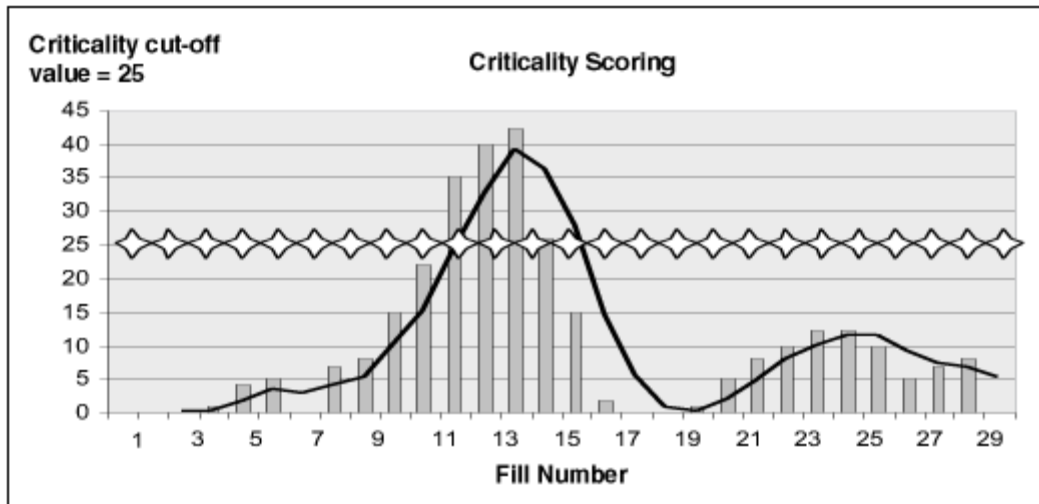


Quality Risk Assessment for Environment Monitoring

risk of problematic environmental monitoring situations or results.

Figure 19

Graph of Criticality Scores



Article Acronym Listing

- CAPA Corrective and Preventive Action
- CCP Critical Control Point
- CFU Colony Forming Unit
- cGMP Current Good Manufacturing Practice
- FMEA Failure Mode and Effects Analysis
- FMECA Failure Mode, Effects, and Criticality Analysis
- FTA Fault Tree Analysis
- HACCP Hazard Analysis and Critical Control Point
- HAZOP Hazard Operability Analysis
- HEPA High Efficiency Particulate Air
- HVAC Heating, Ventilation, and Air-Conditioning
- ISO International Organization for Standardization
- MPRM Modular Process Risk Model
- QA Quality Assurance
- QC Quality Control
- QMRA Quantitative Microbiological Risk Assessment
- SRA System Risk Analysis
- UDAF Uni-Directional Air Flow
- USP United States Pharmacopoeia