Steps to Ensuring a Successful Audit: Effective Risk Assessment Design

Abstract

When designing a process, product quality is an important measure of success. To ensure product quality, it is imperative that the environment is monitored for contamination. The best way to locate sources of contamination is via risk assessment, best performed before a process has been implemented. There are multiple tools to assist in completing a risk assessment, and once completed, it is imperative to continually update this body of knowledge to guarantee a defensible monitoring program is developed and enacted.

Introduction

When related to Environmental Monitoring (EM), risk management often refers to a complete understanding of how often and how severe a process can be affected by external factors. The development of this knowledge, a risk assessment, is the culmination of multiple party's efforts, including Quality Engineers, Microbiologists, and Production staff. Actions involved in completing a risk assessment start at the very beginning of new cleanroom construction with the identification of product impact sources. The relative risk to product quality is given hierarchy using well-established assessment tools.

In order to prepare for this process, it is important to attain a strong base of EM knowledge.

Monitoring Basics

EM typically includes the tracking and enumeration of both viable and nonviable particles. Viable particles include living things, such as bacteria, molds and yeasts. The group of nonviable particles is comprised of everything non-living, including but not limited to dust, hair, smoke and even particles as small as molecular compounds, such as chlorides or amines. Both types of contamination originate from multiple sources, such as personnel, surfaces and the surrounding air.

Critical areas are often monitored for the purpose of ensuring a specified level of product quality.

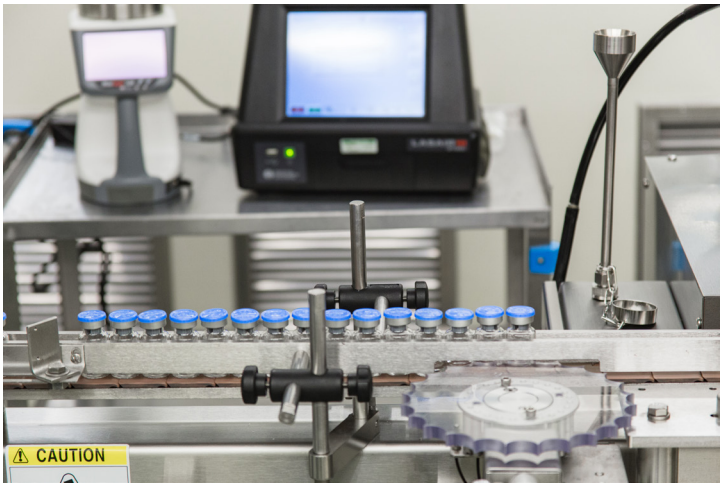

Figure 1 *MiniCapt® Mobile Microbial Air Sampler and Lasair® III Aerosol Particle Counter placement adjacent to filling line*

When levels of product quality deviate outside the specified level, which are determined by risk assessment, the results are categorized into three types of failures:

- Out-of-specification (OOS): the result falls outside of establish acceptance criteria, determined by risk assessment and regulatory bodies.
- Out-of-expectation (OOE): the result is atypical within a series of results obtained over a short period, but meets specifications
- Out-of-trend (OOT): the result is outside the predictive model and may fail process control tests

Similar to product quality, contamination can deviate outside of acceptable levels and impact product results. The acceptable levels of contamination are determined in the same way: with a risk assessment. With EM, sources of contamination can be quickly identified, leading to a speedier recovery of the process with less downtime. EM also assists with the resulting investigations that occur when a OOS, OOE and OOT is found.

Risk Assessment Tools

FDA and European authorities have made risk assessment mandatory, with supporting document *ICH Quality Risk Management Q9*. Methods for performing a risk assessment should fit the need, and several options are available.

FMEA

Failure Mode Effect Analysis (FMEA) is the ideal risk assessment tool to use for process management. Failures likely to occur during manufacturing or during a filling operation for example, are categorized by severity, occurrence, and detection ability. The categorization is used to develop a score providing a numeric representation of risk sources.

An example of FMEA score calculation is below.

A score system is determined to be equal to and between numbers 1 and 5, with 1 being 'low', and 5 being 'high'.

Points of risk are identified and given a score. Risk point 1 and its final FMEA score calculation is determined:

RP1: (2) severity, (5) occurrence, (5) detection ability

2 x 5 x 5 = 50 = FMEA final score

HACCP

Hazard Analysis Critical Control Points (HACCP) is the assessment tool often used for non-sterile products, such as food. It is less statistical and focused more on the entire process as a whole.

Others

At least a dozen more tools exist, allowing for personalized risk assessment construction to fit the needs of multiple industries.

Criticality Factors

Locations in manufacturing environments associated with a rating system with adjusted monitoring frequency are defined as criticality factors. The range of value categories are determined on an individual basis, aligning with the needs of the particular process under evaluation. For example, a location with a criticality factor of 1 (set to be the highest risk level), is determined from a risk assessment to have a monitoring frequency of daily or after each batch. From this location's criticality factor, surrounding areas are also evaluated (see **Table 1**).

Table 1. Example of criticality factor and monitoring frequency by location

Criticality Factor	Location	Monitoring Frequency
1	ISO 5, filling points	Daily or each batch
2	ISO 7, surrounding of ISO 5 ISO 7, gowning rooms	Weekly
3	ISO 5, depyrogenation tunnels	Weekly
4	ISO 8, preparation areas	Monthly
5	ISO 9, sterilization/washing areas	Every four months

Table 1 is determined from a set of decision criteria, including but not limited to the following:

- cleanliness needs of the locations
- personnel transit
- incoming goods
- component preparation
- activity duration
- room temperature
- wet/dry areas
- open/closed process
- final formulation/filtration
- variations within rooms (active air, surface samples, etc.)
- sampling criticality (ex. high sampling frequency creates more contamination with operator intervention)

Closer Look: Assessing Risks to Product Fills

It is imperative that the appropriate method is chosen to monitor contamination. Older methods, such as passive monitoring with settle plates, once standard practice, are obsolete.

Let's take a look at a typical example of post-fill assessment using settle plates using Whyte's method. In this method, contamination rate is determined based on the total count and the ratio of product and settle plate area and exposure. The result is categorized into low, medium or high risk. The example values given below are very commonly found.

Figure 2 *Passive air monitoring (settle plates)*

- Settle plate count = 1 CFU
- Settle plate area (90 mm) = 64 cm^2
- Settle plate exposure = 240 minutes
- Product area = 1 cm^2
- Product exposure = 1 minute

Contamination rate (%)=

Settle plate count x [(Product Area x Product exposure) / (Settle plate area x Settle plate exposure)] x 100

= 1 x [(1 x 1) / (64 x 240)] x 100 = **0.0065 %**

Table 2. Risk associated with range of contamination rates

Contamination Rate	Risk
< 0.03%	Low
> 0.03 - 0.09%	Medium
≥ 0.1%	High

A result of 0.0065% would be placed in the 'low' risk category (**Table 2**). However, settle plates have been proven to be unsuitable for ISO 5 monitoring due to lack of validation. Active air and continuous monitoring techniques are the preferred method for ISO 5 environments. Specific examples, such as the MiniCapt Mobile and BioCapt® Single Use, have been validated to ISO 14698 with data proving high biological and physical efficiency.

When determining which method to use, ask yourself how reliable you expect the results to be. If no variance to contamination rates are observed, how valuable is the test? Should other methods be used? Do the alternate method results conflict? These questions must be answered to achieve a comprehensive and defensible monitoring program.

Figure 3 *BioCapt® Single Use*

After a Risk Assessment

The entire process of performing a risk assessment can take weeks to months to complete, with an average of one week per filling line. Once the assessment has concluded, sampling rationale that supports the locations and monitoring frequency are worked into Standard Operating Procedures (SOPs) and used to determine viable and total particle counter installations. Final documentation of risk assessment conclusions are essential for successful audits and investigations, because your practices have a firm backing and have been tested and proven to be sufficient for your needs. It is recommended that risk assessments be continually performed and rationales and procedures be constantly criticized and improved. Constant innovation and improvement must be part of company culture.

Conclusion

From regulations required by the FDA and European authorities, risk assessments are a mandatory part of process development and understanding. Risk assessments performed to ensure quality assist in identifying risk to the process, management of that risk, and controlling/monitoring scheme development. Assessments should be performed prior to process implementation, not after, allowing for proper installation of monitoring devices.

By taking the necessary steps to complete a risk assessment, you can ensure a defensible monitoring program that helps facilitate audits and investigations.

Particle Measuring Systems offers a wide array of consultancy services. Contact us for more information.

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